The American Journal of Medicine

nia Hospital
anniversary

Duncan, M.D.

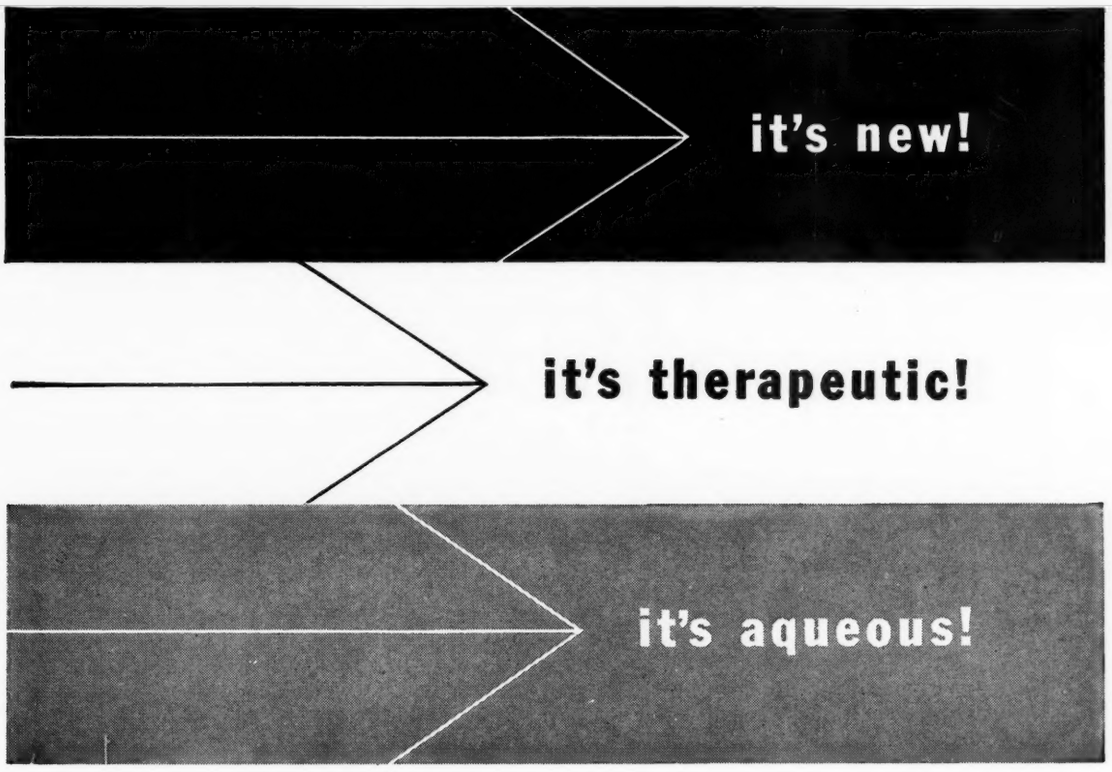
ber 1951

The American Journal of Medicine

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 19, N. Y. Yearly Subscription, $12.00 U. S. A.; $14.00 Canada and Latin American countries; $15.00 Foreign. Single Numbers $2.00; Symposia Numbers $4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. November, 1951—Volume XI, No. 5.

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 19, N. Y. *Style for bibliography*: Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

Change of address must reach us one month preceding month of issue.



vi-aqua therapeutic

AQUEOUS MULTIVITAMIN THERAPEUTIC CAPSULES

faster, more certain, more complete utilization

1. more certain absorption, particularly in conditions associated with poor fat absorption (dysfunction of the liver, pancreas, biliary tract and intestine).
2. faster recovery from deficiencies with speedier convalescence in medical and surgical patients.
3. 100% natural vitamin A, therapeutic activity proven by clinical use over many years (contains no synthetic A).
4. no fish taste or odor (special processing removes fish oils and fats); well tolerated even by sensitive patients.

Each VI-AQUA THERAPEUTIC CAPSULE provides:

AQUEOUS	
Vitamin A* (natural)	12,500 Units
Vitamin D* (calciferol)	1,000 Units
Ascorbic Acid (C)	150 mg.
Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	5 mg.
Vitamin B_{12}	2 mcg.
Niacinamide	100 mg.
Pyridoxine HCl (B_6)	1 mg.
d, Calcium Pantothenate	10 mg.
dl, Alpha-Tocopheryl Acetate (E)*	5 mg.

*oil-soluble vitamins made water-soluble with sorethytan esters; protected by U.S. Patent 2,417,299.

REQUEST SAMPLES AND LITERATURE FROM...

U. S. VITAMIN CORPORATION
CASIMIR FUNK LABORATORIES, INC. (affiliate)
250 EAST 43rd ST., NEW YORK 17, N.Y.

★ *Epileptic Men of Genius* ★

One of the greatest military leaders and statesmen of all times, Arthur Wellesley Wellington, is said to have suffered from attacks of epilepsy during his adult life.

Comparative studies have shown that in some cases better control of grand mal as well as petit mal seizures can be obtained with Mebaral than with corresponding doses of other antiepileptic drugs. Mebaral produces tranquillity with little or no drowsiness. It is particularly desirable not only in epilepsy but also in the management of anxiety states and other neuroses. The fact that Mebaral is almost tasteless simplifies its administration to children. Average dose for children ½ to 3 grains, adults 3 to 6 grains daily. Tablets ½, 1½ and 3 grains.

MEBARAL®
Brand of Mephobarbital

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY

Winthrop-Stearns INC.
NEW YORK 13, N. Y. WINDSOR, ONT.

Trademark registered U. S. & Canada

CONTENTS

The American Journal of Medicine

Vol. XI NOVEMBER, 1951 No. 5

PENNSYLVANIA HOSPITAL—200th ANNIVERSARY

Introduction

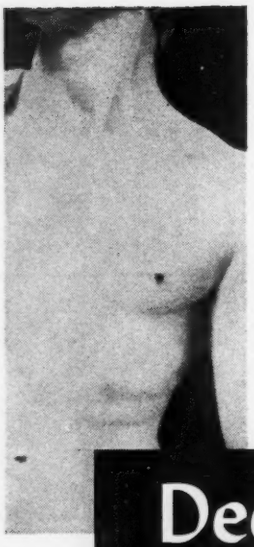
Reprints of Historical Interest

Two Recent Reprints from the Pennsylvania Hospital

Lectures Given at Bicentennial Exercises

The bicentennial of the Pennsylvania Hospital, first to be founded in this country, is a significant milestone in the development of American medicine, to which this issue of The American Journal of Medicine is dedicated. Dr. Duncan, Director of the Medical Division of the Pennsylvania Hospital, and Guest Editor of this issue, has arranged an interesting commemorative program.

Contents continued on page 5



the NEW therapy in "functional G. I. distress"...

Decholin with Belladonna

Patients complaining of gastrointestinal distress without detectable organic cause are common problems in daily practice. By combining spasmolytic action with improvement in liver function, *Decholin/Belladonna* — in such cases — gives symptomatic relief by

reliable spasmolysis

hydrocholeretic flushing of biliary tract

improved blood supply to liver

mild, natural laxation without catharsis

While of special value in functional dyspepsia, *Decholin/Belladonna* is, of course, treatment of choice in biliary tract disorders for thorough and unimpeded flushing of the biliary system.

DOSAGE: One or, if necessary, two *Decholin/Belladonna* tablets three times daily after meals.

PACKAGING: *Decholin* (brand of dehydrocholic acid) *with Belladonna*, bottles of 100 tablets. Each tablet contains dehydrocholic acid 3¾ gr. and belladonna ⅛ gr. (equivalent to tincture of belladonna, 7 minims).

Decholin, trademark reg.

AMES

AMES COMPANY, INC., ELKHART, INDIANA

AMES COMPANY OF CANADA, LTD., TORONTO

DB-1

CONTENTS

The American Journal of Medicine

Vol. XI NOVEMBER, 1951 No. 5

Contents continued from page 3

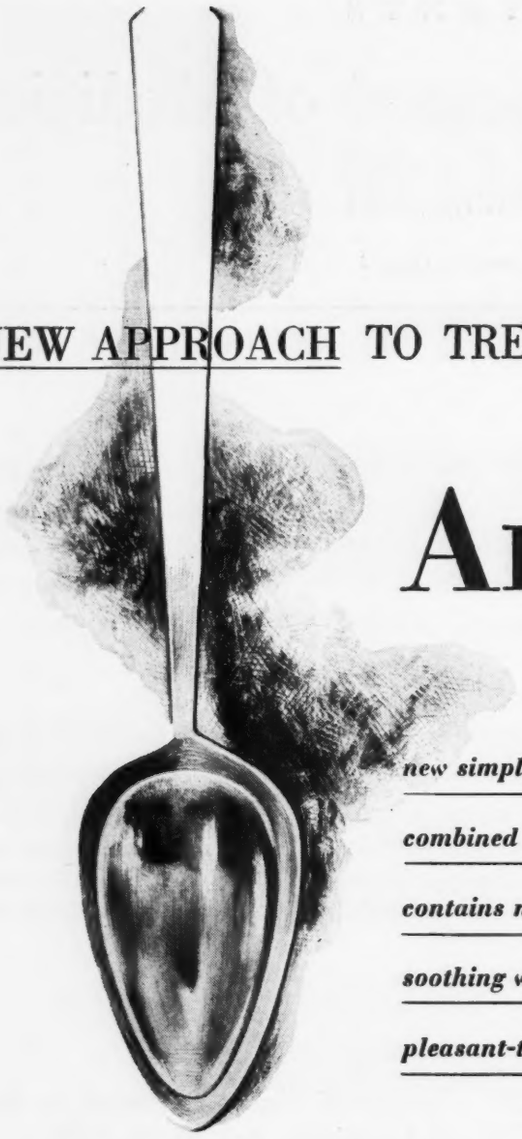
Review

Seminars on Arteriosclerosis

Research Society Abstracts

Case Reports

Contents continued on page 7



NEW APPROACH TO TREATMENT OF COUGHS!

Antosen

Squibb Liquid Cough Sedative

new simplified formula of two essential ingredients

combined sedative—anti-secretory effect

contains no expectorants

soothing without excessive drowsiness

pleasant-tasting, fruit-flavored

Antosen is for coughs due to common colds or associated respiratory infections. Useful also as a sedative base to which expectorants and/or other drugs may be added. Supplied in pints and gallons.

contains per fluid ounce:

Prophenpyridamine maleate	25 mg.
Codeine phosphate	65 mg.
Alcohol	5%

SQUIBB

CONTENTS

The American Journal of Medicine

Vol. XI NOVEMBER, 1951 No. 5

Contents continued from page 5

Change of address must reach us one month preceding month of issue.

fair, fat, and flatulent

coltish, cozy, and crapulous

dull, dragged out, and dyspeptic

bald, bearish, and bloated

bored, buxom, and bilious

Problem Patients ***five of a kind . . .***

Perhaps it's a sign of the times. Or possibly it just happens that certain patients are more vocal than others. But in either event, chronic "indigestion" seems on the way to becoming the No. 1 occupational hazard among a familiar coterie of confirmed escapists whose talent is self-delusion, and whose common lament is anent cardialgia, dyspepsia, and gas on the stomach.

There's no one way to handle these middle-aged worriers and hurriers, mopers and topers, and similar dupes of indulgence. But it's often said that the "commonest cause" of digestive distress in patients over forty is low grade biliary dysfunction. And such being the case, Depancol can serve an important two-fold purpose: (1) By affording prompt relief from presenting complaints — flatulence, biliousness, and so forth — Depancol helps to enlist the patient's early cooperation in the essential long-range program to correct bad habits; (2) By physiologically flushing and stimulating the sluggish biliary system, Depancol serves to encourage restoration of normal biliary function.

Depancol®

Dehydrocholic Acid	⅓ gr.
Bile Salts	1½ gr.
Pancreatic substance equivalent to Pancreatin U.S.P.	4½ gr.

in an enteric coated tablet

Note: no laxatives

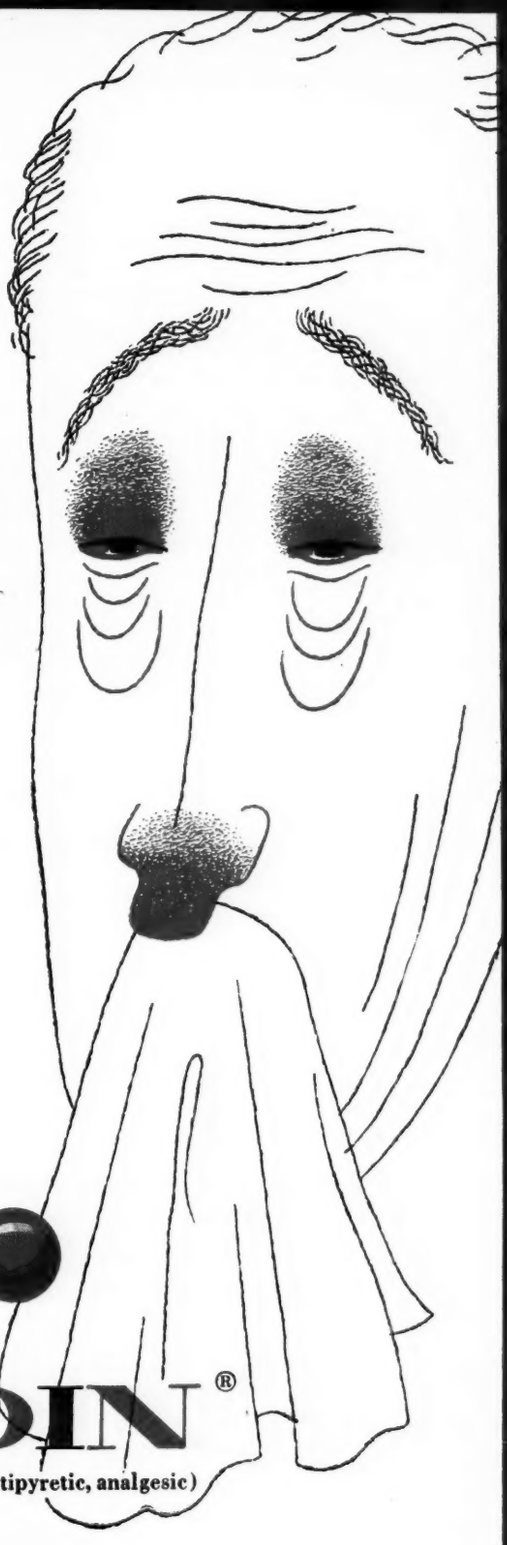
SUPPLY Bottles of 50, 500, and 5,000 enteric coated tablets, available at your druggist.

DOSAGE Average: 1 or 2 tablets 3 times daily, with or after meals.

CHILCOTT *Laboratories*

DIVISION OF The Maltine Company

MORRIS PLAINS, NEW JERSEY



the sooner - CORICIDIN

the better - CORICIDIN

Greatest likelihood of aborting and mitigating symptoms of the common cold follows *early* use of CORICIDIN. Containing chlorprophenpyridamine maleate — the antihistamine that is effective in the smallest dosage — CORICIDIN is gratifyingly devoid of significant side effects.

CORICIDIN®

(antihistamine, antipyretic, analgesic)

Schering CORPORATION

Bloomfield, New Jersey

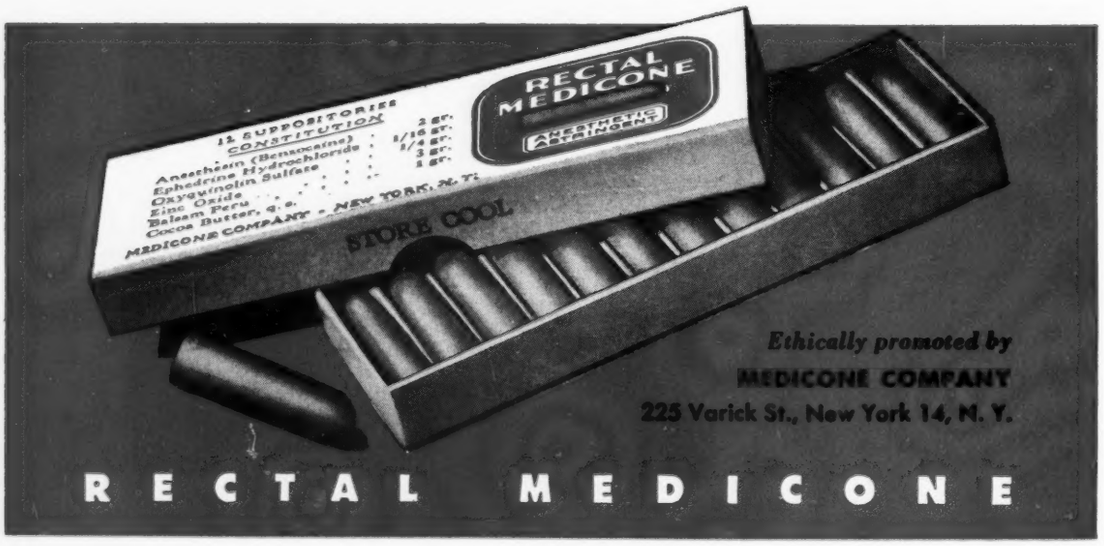
CORICIDIN

Clinical success in postpartum hemorrhoids

From a clinical report of 79 cases of postpartum hemorrhoids, treated with RECTAL MEDICONE at a large New York institution, the following results were tabulated:

NO. OF CASES	TYPE	RESULTS
41	SUBACUTE	38 SATISFACTORY RESPONSE
22	ACUTE	22 RELIEF IN ALL CASES
16	CHRONIC	10 SATISFACTORY RESPONSE *(4 of the 16 cases required surgery)*

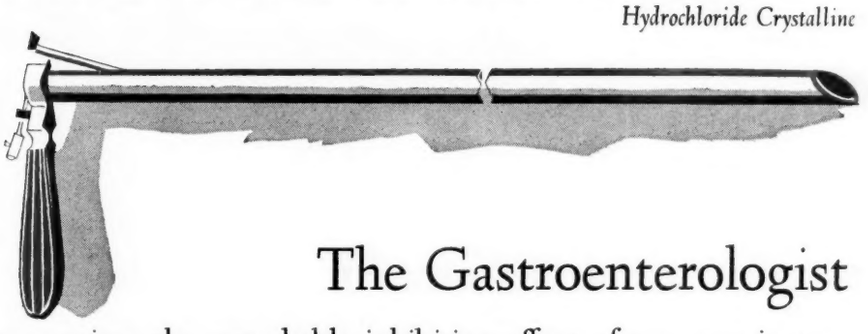
The explanation for these highly favorable results in this painful condition lies in the fact that RECTAL MEDICONE SUPPOSITORIES contain benzocaine for topical anesthesia — reinforced by other effective anti-hemorrhoidal agents, which promote retrogression and healing.



Effective against many bacterial and rickettsial infections, as well as certain protozoal and large viral diseases.

AUREOMYCIN

Hydrochloride Crystalline



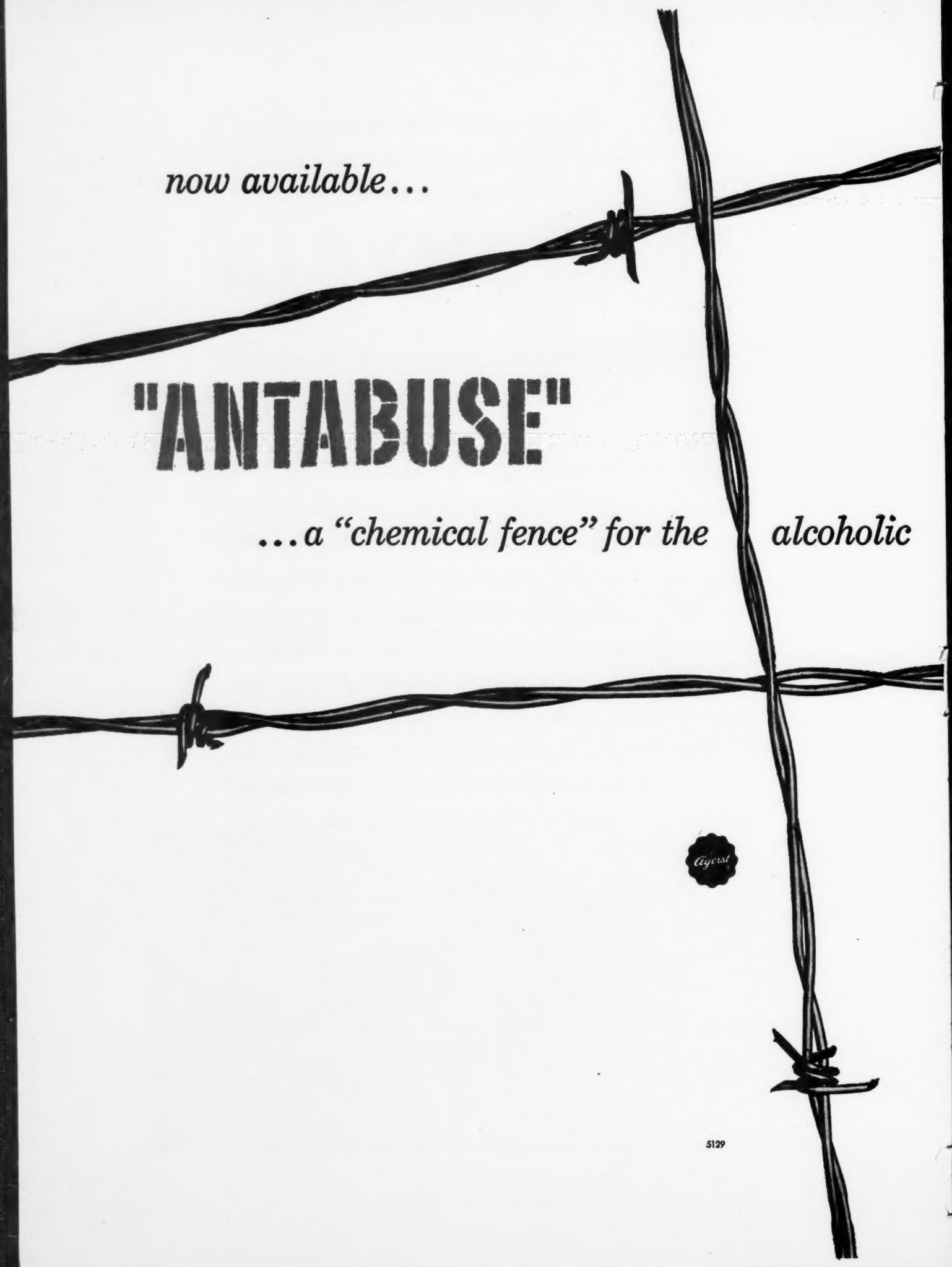
The Gastroenterologist

recognizes the remarkable inhibiting effect of aureomycin on a great number of organisms, especially those commonly found in the gastrointestinal tract. It is of great value in the preparation of patients for surgery of the bowel or biliary tract, as well as in the medical management of infections in these areas. Aureomycin is also highly effective in intestinal amebiasis. Aureomycin is peculiarly adapted to the treatment of many biliary and hepatic infections, because of the high concentrations it attains in the bile and because of its protection of the hepatic parenchyma from bacterial necrosis. Aureomycin is indispensable in gastroenterology.

Packages

Capsules: Bottles of 25 and 100, 50 mg. each capsule. Bottles of 16 and 100, 250 mg. each capsule.
Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. distilled water.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
30 Rockefeller Plaza, New York 20, N.Y.


now available...
"ANTABUSE"
...a "chemical fence" for the alcoholic
Ayerst
5129

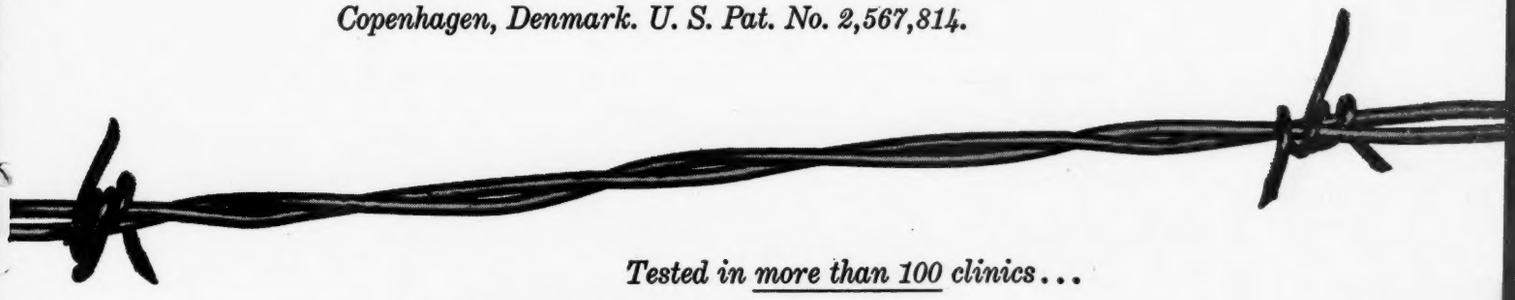
Much has been written about "Antabuse." Many alcoholics have long awaited its benefits.

Now, after nearly three years of intensive clinical research, it is available for prescription use.

"Antabuse" sets up a sensitizing effect to ethyl alcohol. It builds a "chemical fence" around the alcoholic . . . helps him develop a resistance to his craving. Its high degree of efficacy is confirmed by extensive clinical evidence.

"Antabuse" is safe therapy when properly administered. However, it should be employed only under close medical supervision. Complete descriptive literature is available and will be gladly furnished on request.

"Antabuse" is identical with the material used by the original Danish investigators, and is supplied under license from Medicinalco, Copenhagen, Denmark. U. S. Pat. No. 2,567,814.



Tested in more than 100 clinics . . .
by more than 800 qualified investigators . . .
on more than 5,000 patients . . . and covered by
more than 200 laboratory and clinical reports.

"ANTABUSE"®

. . . brand of specially prepared and highly purified tetraethylthiuram disulfide.

Supplied in tablets of 0.5 Gm., bottles of 50 and 1,000.

Ayerst, McKenna & Harrison Limited • New York, N. Y. • Montreal, Canada

STATEMENT OF OWNERSHIP

STATEMENT OF THE OWNERSHIP, MANAGEMENT, AND CIRCULATION REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946 (Title 39, United States Code, Section 233)

Of The American Journal of Medicine, published monthly at New York, N. Y., for Oct. 1, 1951.

1. The names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, The American Journal of Medicine, Inc., 49 W. 45th Street, New York 19, N. Y.; Editor, Alexander B. Gutman, M.D., College of Physicians & Surgeons, 620 W. 168 St., N. Y. 32; Managing editor, Florence A. Wey, 36 East 36th Street, New York 16, N. Y.; Business manager, Pliny A. Porter, 107 Woodcrest Ave., White Plains, N. Y.

2. The owner is: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual member, must be given.) The American Journal of Medicine, Inc., 49 West 45th Street, New York 19, N. Y.; M. T. Wisotzkey, President and Sole Owner, 20 East 74th Street, New York 21, N. Y.

3. The known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages, or other securities are: (If there are none, so state.) None.

4. Paragraphs 2 and 3 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting; also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner.

5. The average number of copies of each issue of this publication sold or distributed, through the mails or otherwise, to paid subscribers during the 12 months preceding the date shown above was:

(This information is required from daily, weekly, semiweekly, and triweekly newspapers only.)

M. T. WISOTZKEY, President

Sworn to and subscribed before me this 10th day of September, 1951

ROSE V. CELENTANO

[SEAL]

(My commission expires March 30, 1952.)

A Significant Development

COMPE

A NEW PENICILLIN SALT

Compenamine, an entirely new penicillin compound, is the penicillin G salt of the levo isomer of N-methyl-1,2-diphenyl-2-hydroxyethylamine. Its generic name is *l*-ephenamine penicillin G. It is less soluble in water than is procaine penicillin, and its theoretical potency is 1,058 units per mg.

AS EFFECTIVE AS PROCAINE PENICILLIN G

The action of Compenamine, unit for unit, was found to be identical with that of procaine penicillin G against 73 strains of bacteria, six viruses, and five protozoa. Absorption and excretion curves are essentially the same for both penicillin salts, but longer blood levels are usually found with Compenamine.

SIGNIFICANT REDUCTION OF ALLERGIC REACTIONS

On the basis of extensive clinical experience,[1,2,3,4,5,6,7] Compenamine has been shown to be well tolerated even by patients sensitive to procaine penicillin G. In known reactors, in excess of 80 per cent can tolerate this salt without reaction. In over 1,000 cases, initial intradermal or topical use, followed by a large challenging dose 10 days later, *did not lead to induced sensitivity in a single instance.* In this series, only seven instances of allergic reactions were seen, less than one per cent. *Thus Compenamine greatly broadens the applicability of penicillin therapy.*

---

1. Longacre, A.B.: P-92 Penicillin; Report of a Very Low Reaction Rate in Therapy with a New Penicillin Salt, Antibiotics & Chemotherapy *1*:223 (July) 1951.
2. Kadison, E.R.; Ishihara, S.J., and Waters, T.: A New Form of Penicillin, with Anti-allergic Properties, Am. Pract. & Dig. of Treat. 2:411 (May) 1951.

PERSONAL COMMUNICATIONS

3. Lupton, A.: Presbyterian Hospital, New York.
4. Wooldridge, W.: Barnard Skin & Cancer Hospital, St. Louis.
5. Katz, S.: Gallinger Municipal Hospital, Washington, D.C.
6. Suskind, R.: Cincinnati General Hospital.
7. Finnerty, E.J., Jr.: Boston City Hospital.

in Penicillin Therapy....

NAMINE

INDICATIONS

Compenamine is indicated in the treatment of all conditions responding to penicillin. Since it is nearly insoluble in water and in oil, its dosage forms are of the repository type, leading to prolonged blood levels. Hence it makes possible once-a-day injection in most patients.

NO PRICE PENALTY TO YOUR PATIENTS

Compenamine costs no more than comparable dosage forms of procaine penicillin G, giving your patients all the advantages of this new penicillin salt without price penalty.

MERITS ROUTINE USE

Because it significantly reduces the incidence of allergic reactions, because its therapeutic efficacy is as great as that of procaine penicillin G, and because it imposes no price penalty, Compenamine merits routine use whenever a repository type of penicillin is called for.

AVAILABLE IN THREE DOSAGE FORMS

Compenamine is currently available in three repository dosage forms:

Compenamine (for aqueous injection), in vials.

Compenamine Aqueous, in vials and disposable and permanent syringe cartridges.

Compenamine in Peanut Oil, in vials and disposable and permanent syringe cartridges.

Other dosage forms will be announced shortly.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION, NEW YORK 17, N.Y.

THE FIRST PRODUCER OF CRYSTALLINE PENICILLIN G IN COMMERCIAL QUANTITIES

effective

in hypertension

1
2
3
4

REFERENCES

Freis, E.D.: Veratrum Viride and Hypertension, Correspondence, J.A.M.A. *144:* 1023 (Nov.18) 1950.

Wilkins, R.W.: Veratrum Viride and Essential Hypertension, New England J. Med. *242*:535 (Apr. 6) 1950.

Gropper, A.L.; Surtshin, A., and Hedrick, J.T.: Effects of Veriloid on Essential Hypertension, A.M.A. Arch. Int. Med. *87*:789 (June) 1951.

Yonkman, F.F. Neurogenic Hypertension, Chemical Approaches to Its Amelioration, J. Michigan M. Soc. *50*:160 (Fed.) 1951.

A potent hypotensive principle biologically standardized in mammals

Veriloid is probably the most effective hypotensive agent available today.[1] Its characteristic effect, with careful administration, appears to be one of moderation rather than elimination of the hypertension.[2] The therapeutic ratio of Veriloid is relatively high, and long-continued treatment is possible because its administration does not produce idiosyncrasy or tolerance in most patients treated.[2,3,4]

In one study, the administration of Veriloid brought striking relief from hypertension and its disturbing discomforts in 80 per cent of patients with essential hypertension.[2] Veriloid controlled the blood pressure and produced a gratifying, beneficial effect, even after the failure of other hypotensive drugs in malignant hypertension in the preuremic stage and in hypertensive encephalopathy.[1,2] Veriloid has been found to control neurogenic hypertension, even after refractoriness to ganglionic blocking agents had developed.[4]

VERILOID*

Clinical experience shows that Veriloid is effective in all forms of hypertension—mild, moderate and severe, and gratifying objective as well as subjective results follow its administration.

DOSAGE: The usual daily requirement of Veriloid is 9 to 15 mg., given in divided dosage three times daily, every 6 to 8 hours, the first dose to be taken after breakfast. The evening dose should be 1 or 2 mg. larger than the other two doses of the day. However, requirements for Veriloid vary from patient to patient, and in most individuals periodic adjustment in dosage is needed, because with continued administration, patients become more reactive to Veriloid.

Veriloid is available in tablet sizes of 1, 2 and 3 mg., in bottles of 100, 500 and 1,000 tablets.

VERILOID-VPM

Containing Veriloid (2 mg.), phenobarbital (15 mg.), and mannitol hexanitrate (10 mg.), Veriloid-VPM provides valuable sedation and the vasodilating action of mannitol hexanitrate. This combination usually makes possible reduced dosage without sacrifice of therapeutic efficacy. Also, phenobarbital adds the advantage of increasing the spread between effective therapeutic dosage and the dosage at which side reactions occur.

VERILOID WITH PHENOBARBITAL

Veriloid With Phenobarbital (Veriloid, 2 mg., phenobarbital, 15 mg.) provides sedation without the action of mannitol hexanitrate. It is valuable when emotional tension must be controlled.

*Trade-Mark of Riker Laboratories, Inc.

RIKER LABORATORIES, INC.
8480 BEVERLY BLVD. • LOS ANGELES 48, CALIF.

EXTRA PROTECTION

FOR YOUR CARDIOVASCULAR PATIENT

Normal. Capillaries clearly defined; no transudation, hemorrhage, or papilledema.

RUTAMINAL* provides the extra protection of rutin and ascorbic acid...in support of the cardiotonic action of aminophylline, and the sedation of phenobarbital.

Borderline. Capillaries show irregularities, slight transudation. Incipient papilledema.

Abnormal. Capillaries tortuous, with areas of hemorrhage and transudation. Papilledema.

RUTAMINAL...

Whenever aminophylline and phenobarbital are indicated...

*RUTAMINAL is a trademark of Schenley Laboratories, Inc., and designates exclusively its brand of tablets containing rutin, ascorbic acid, aminophylline, and phenobarbital.

SCHENLEY LABORATORIES, INC.
LAWRENCEBURG • INDIANA

***hema-tonic* in a tablet**

For simple but well-rounded therapy of common anemia — for *optimum support* of both hemoglobin and red cell production —

℞ **Cebetinic***

— the new, modern, multiple action hema-*tonic* which provides eight substances, all concerned with hematopoiesis, in a specially constructed, convenient *tablet* form.

In each tablet:

Ferrous Gluconate	5.0 grains
Vitamin B_{12} Factors (*as determined by microbiological assay*)	5.0 micrograms
Folic Acid	0.67 milligram
Thiamine Hydrochloride	2.0 milligrams
Riboflavin	2.0 milligrams
Pyridoxine Hydrochloride	0.5 milligram
Nicotinamide	10.0 milligrams
Ascorbic Acid	25.0 milligrams

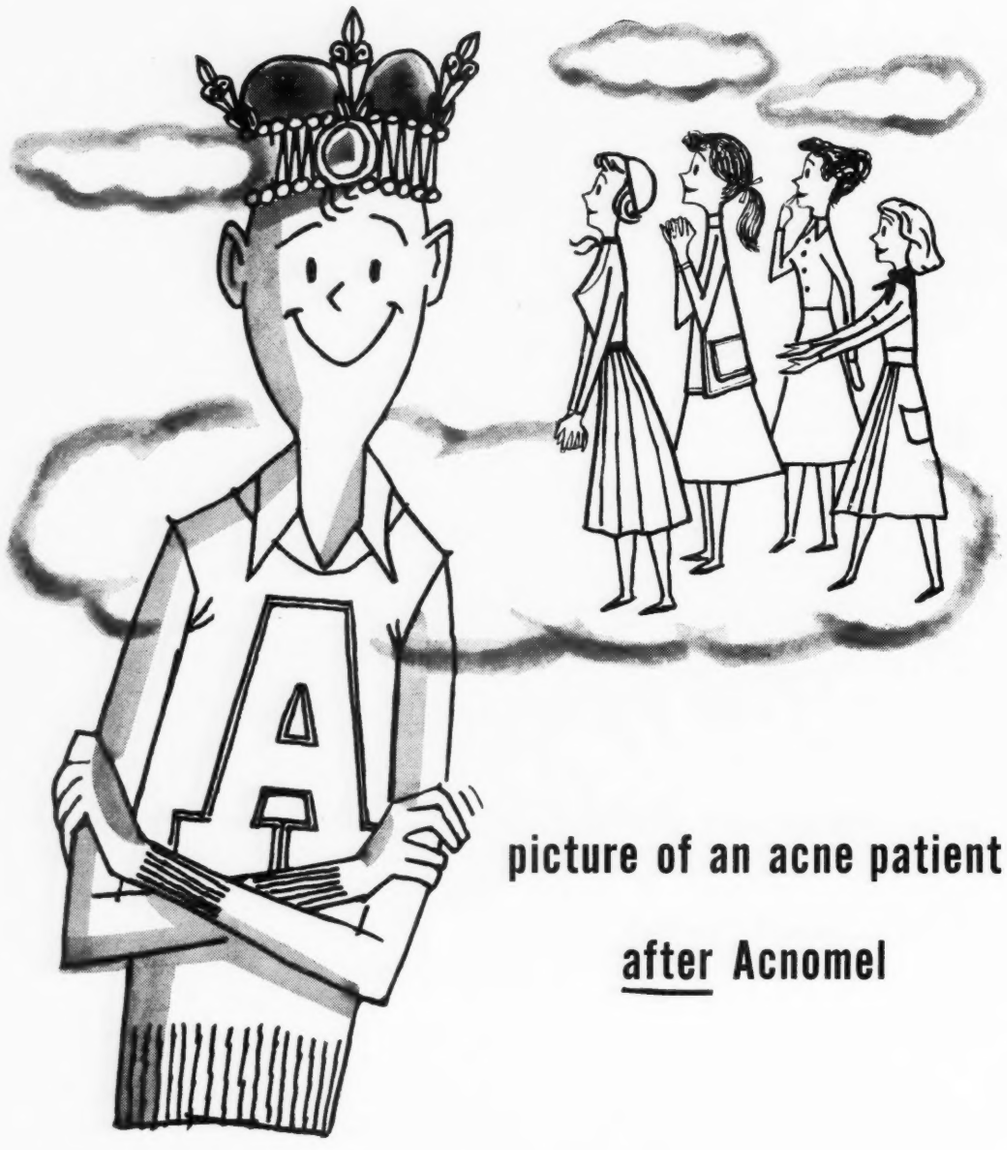
Dosage: Average adult — 3 tablets daily
Children — from 1 to 3 tablets daily

In bottles of 60 and 500 tablets.

*Trademark

Upjohn ***Medicine...Produced with care...Designed for health***

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN



picture of an acne patient

after Acnomel

When you prescribe Acnomel, the complexion-conscious teen-ager receives an immediate "lift" because:

1. Acnomel matches the skin and hides the lesions. Your patient appears in public without the stigma of unsightly blemishes.
2. Acnomel brings dramatic improvement, not in months or weeks, but in a matter of days.

Acnomel is so effective—both therapeutically and cosmetically—that it is prescribed more often than all other ethical acne preparations combined.

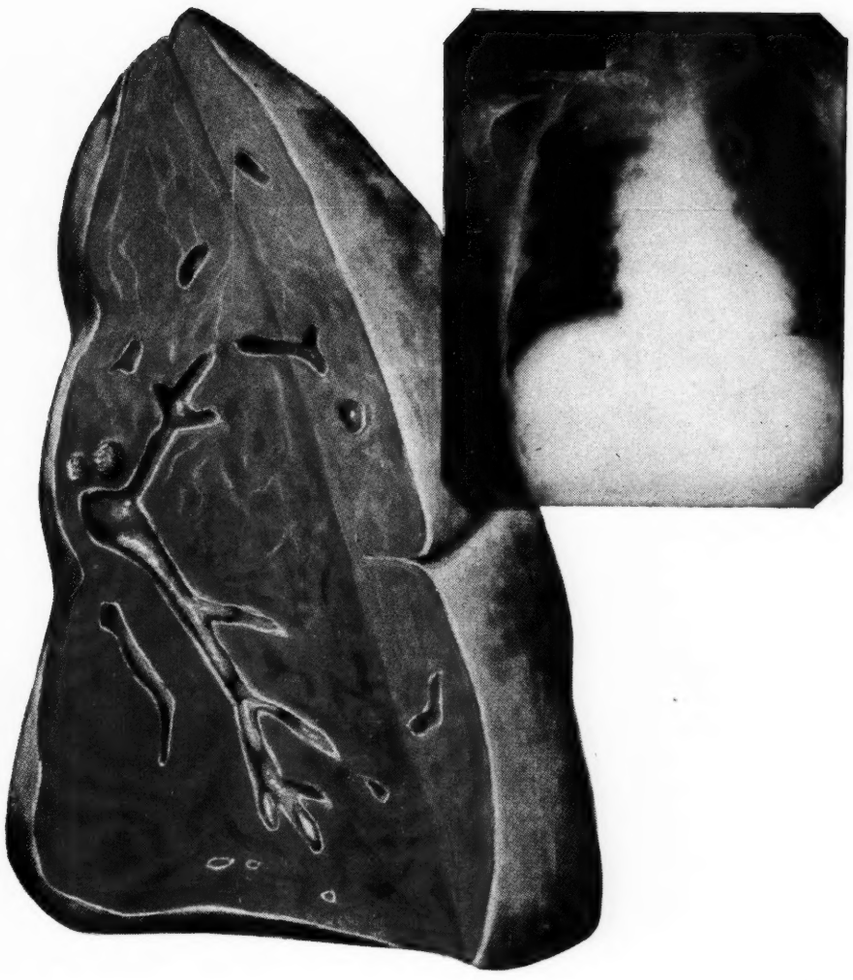
Formula: Resorcinol, 2%; and sulfur, 8%; in a stable, grease-free, flesh-tinted vehicle. Available in specially-lined 1½ oz. tubes.

Smith, Kline & French Laboratories, Philadelphia

Acnomel

a significant advance, clinical and cosmetic, in acne therapy

'Acnomel' T.M. Reg. U.S. Pat. Off.



in primary atypical pneumonia:

"It is our clinical impression, supported by the presented data, that terramycin is the drug of choice in the treatment of atypical pneumonia in infants and children."

Graves, F. B., and Ball, W. O.: J. Pediat. 39:155 (Aug.) 1951

CRYSTALLINE TERRAMYCIN HYDROCHLORIDE

available | *Capsules, Elixir, Oral Drops, Intravenous, Ophthalmic Ointment, Ophthalmic Solution.*

ANTIBIOTIC DIVISION Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

a practical *step forward* in the therapy of rheumatic affections

Pabalate usually provides better therapy for rheumatic affections than pure salicylate itself, through its mutually synergistic combination of para-aminobenzoic acid and salicylate.[1,2] Reports of authoritative clinical tests show a *higher* degree of pain relief... to *more* patients... on *lower* dosage... over *longer* periods... with *greater freedom* from adverse reactions.[3]

REFERENCES: 1. Dry, T. J. et al.: Proc. Staff Meetings Mayo Clin., 21:497, 1946. 2. Hoagland, R. J.: Am. J. Med., 9:272, 1950. 3. Smith, R. T.: J. Lancet, 70:192, 1950.

FORMULA: Each enteric-coated tablet or each teaspoonful of chocolate-flavored liquid contains 0.3 Gm. (5 gr.) sodium salicylate U.S.P., and 0.3 Gm. (5 gr.) para-aminobenzoic acid (as the sodium salt).

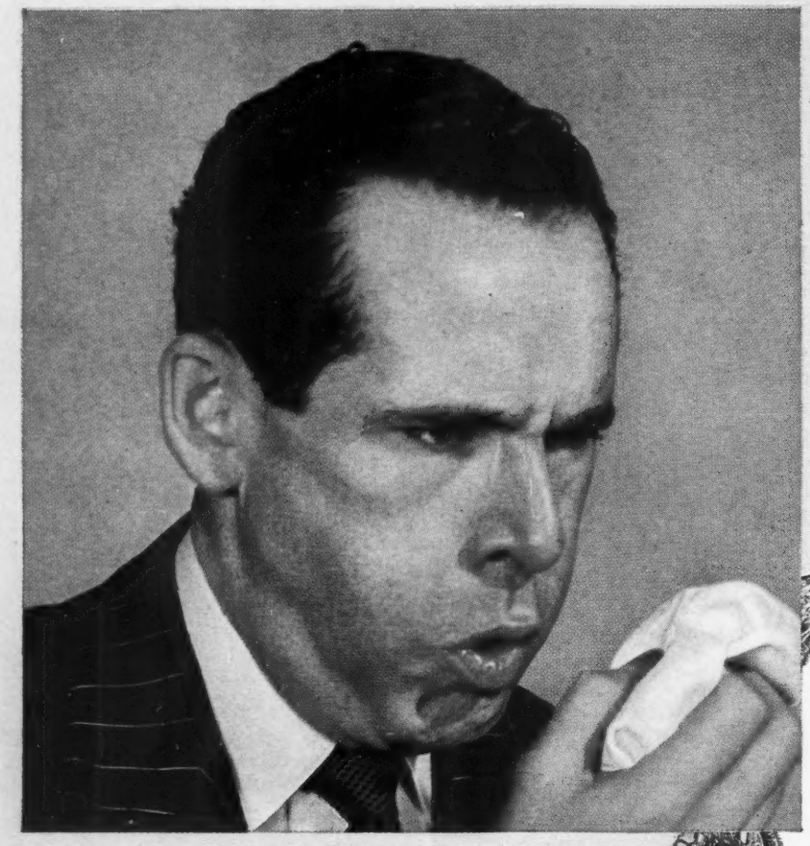
A. H. ROBINS CO., INC.
RICHMOND 20, VA.

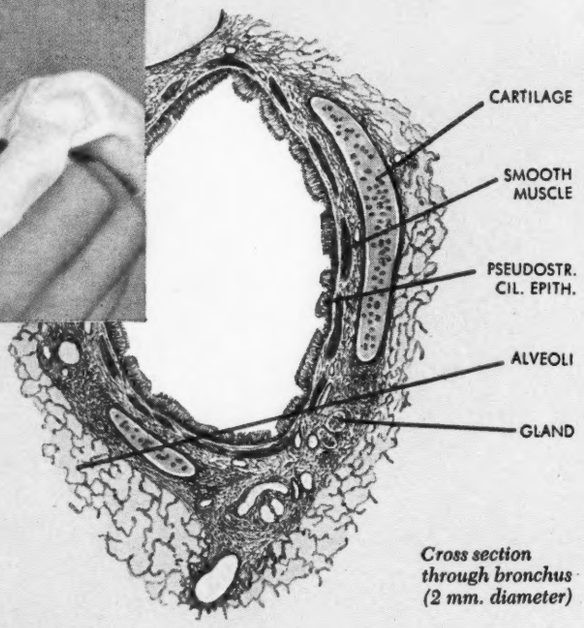
Robins **Pabalate®**

Also available as Pabalate Sodium-Free for cases in which sodium is contraindicated

Seven Years' Research that opened a **New Era**

in Cough Therapy





Cross section through bronchus (2 mm. diameter)

The time encrusted *empirical* approach to cough therapy—with its "picture of confusion, contradiction and neglect"[2]—can now be replaced by sound, *rational* non-narcotic treatment, thanks to the pioneering studies of Boyd et al.,[1,2] demonstrating that glyceryl guaiacolate is the most powerful of expectorants commonly used. Robitussin—the antitussive-expectorant with specific drug action—provides glyceryl guaiacolate for increasing respiratory tract fluid, together with desoxyephedrine, for its bronchial-spasm-relieving[3] and its mood-improving actions—in an aromatic syrup that is highly patient-acceptable.

A. H. ROBINS CO., INC. • RICHMOND 20, VA.

Robitussin®

Robins

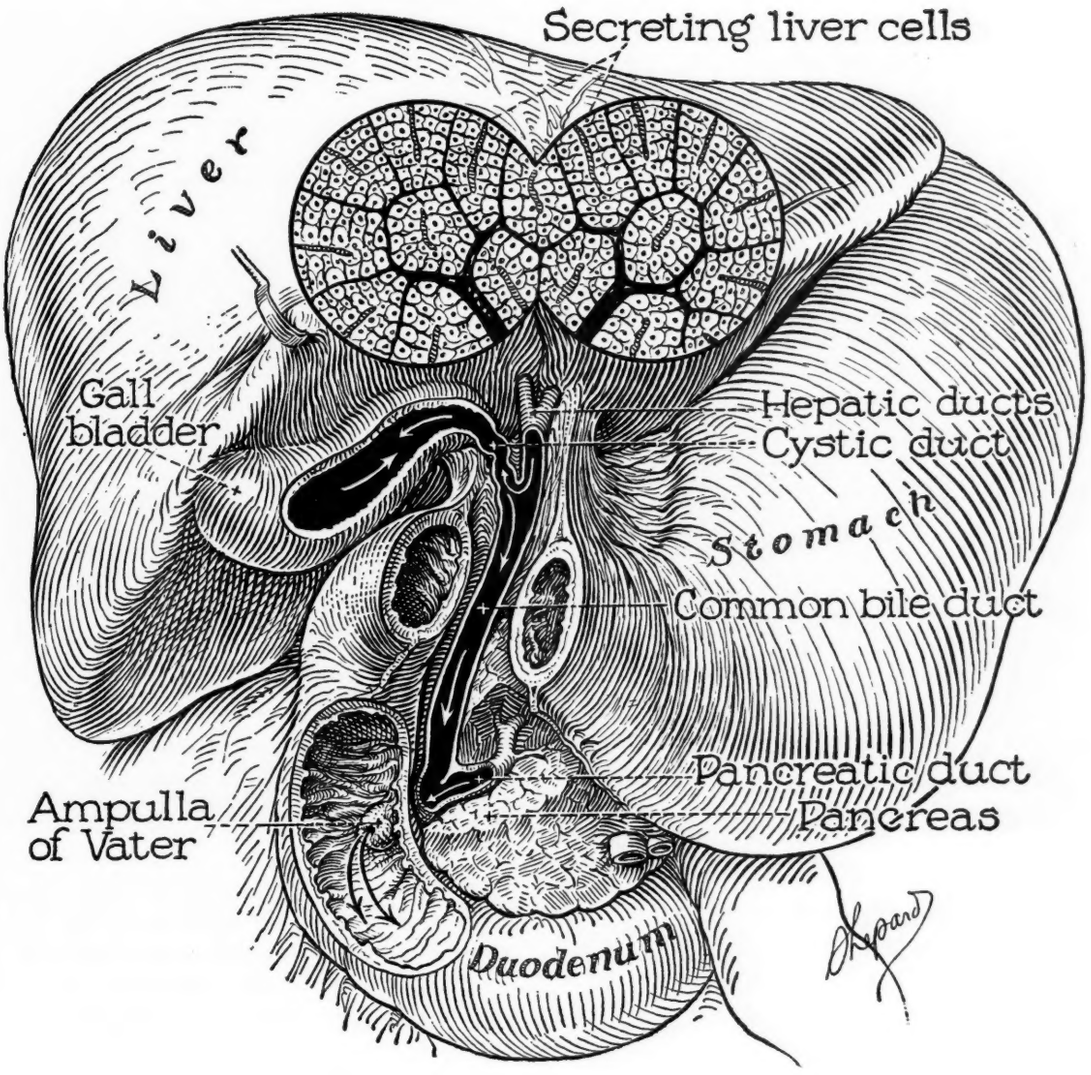
promotes useful cough... minimizes harmful cough

References:

1. Boyd, E. M. and Lapp, S.: J. Pharmacol. and Exper. Therap., 87:24, 1946. 2. Connell, W. F. et al.: Canad. M.A.J., 42:220, 1940. 3. Novelli, A. and Tainter, M. L.: J. Pharmacol., 77:324, 1943.

Formula:

Each 5 cc. (1 teaspoonful) contains 100 mg. glyceryl guaiacolate and 1 mg. desoxyephedrine hydrochloride, in a palatable aromatic syrup.



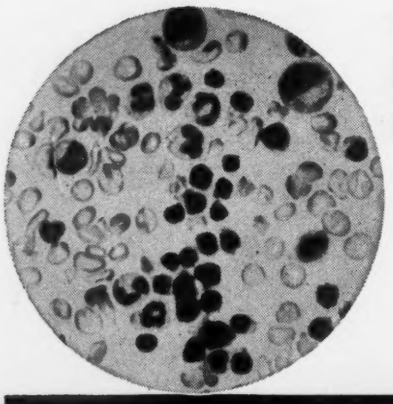
The medical management of gallbladder disease is a physiologic approach to improve hepatic function and to alleviate biliary stasis. The rational regimen of therapy includes:

1. Adjusted diet containing uncooked fats, as tolerated, which induce emptying of the gallbladder.
2. Ketocholanic acids—**KETOCHOL®***—to stimulate the flow of bile and "flush out" the biliary tract.
3. Antispasmodic medication—**PAVATRINE®** with Phenobarbital**—to relax the sphincter of Oddi and allay irritability of the gastrointestinal tract.

*Ketochol combines all four of the oxidized form of the normal bile acids.

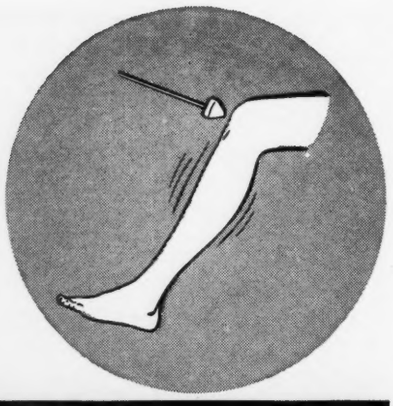
**Pavatrine with Phenobarbital combines the smooth muscle relaxant, Pavatrine, with phenobarbital.

SEARLE RESEARCH IN THE SERVICE OF MEDICINE



For
HEMATOLOGIC
Remission

With
NEUROLOGIC
Response



In pernicious anemia and certain other macrocytic anemias, Crystalline Vitamin B_{12} U.S.P. provides maximum hematologic and neurologic response with microgram dosage. It may be administered either subcutaneously or intramuscularly without pain or discomfort to the patient.

Side effects have not been encountered with Crystalline Vitamin B_{12} and it is the only form of this important vitamin official in the U.S.P. First isolated in the Merck Research Laboratories, Crystalline Vitamin B_{12} is available as Cobione.*

**Cobione is the registered trade-mark of Merck & Co., Inc. for its brand of Crystalline Vitamin B_{12}.*

SUPPLIED: Cobione is supplied in 1 cc. ampuls containing 15 micrograms of Crystalline Vitamin B_{12} U.S.P. in saline solution.

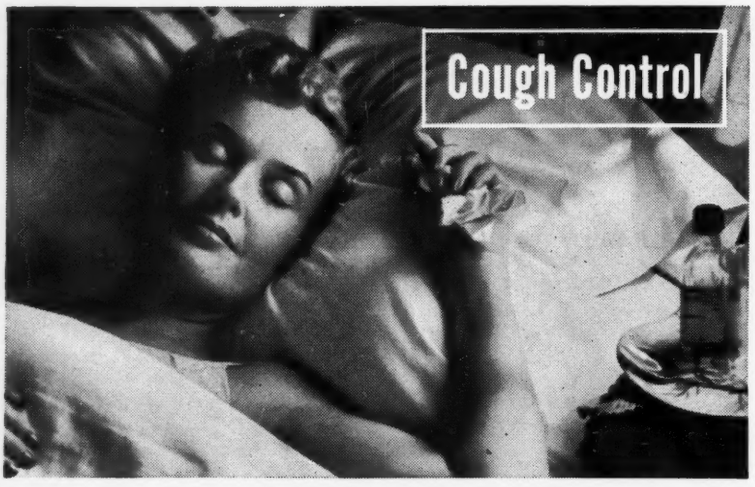
COBIONE®

Crystalline Vitamin B_{12} U.S.P. Merck

COUNCIL ACCEPTED

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited—Montreal

Up-to-Date Antitussive



Sedative-antitussive effects of Methajade control sleep-robbing paroxysmal cough—allow patients to get needed rest.

SUBDUES VIOLENT COUGHING

METHAJADE® spares your patients the needless violence of exhausting, "unproductive" cough—without depriving them of the benefits of normal expectoration.

Because it contains *methadone*, the synthetic analgesic-antitussive, METHAJADE is capable of suppressing the irritability of the cough reflex without blocking it entirely.

Because it contains potassium citrate and diluted phosphoric acid, METHAJADE promotes the liquefaction and loosening of mucus, facilitating the expulsion of bronchial exudate and debris.

Because it relaxes smooth muscle, including that in the tracheobronchial tree, METHAJADE is effective in relieving the bronchial spasm often associated with coughs.

Together, these actions tend to *decrease* the frequency and *increase* the efficiency of coughing, and to relieve bronchial spasm. METHAJADE is therefore well qualified as a practical aid in achieving the modern objectives of cough control:

(1) *to* preserve *the natural physiologic benefits of the cough—*
(2) *to* reserve *the act of coughing for "productive" expectoration.*

Composition—METHAJADE is a sugar-free antitussive with a delicious, fresh, lime flavor. Each 30 cc. (1 fl. oz.) contains:

Methadone hydrochloride* ..... (*d,l*-6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride) WARNING: may be habit forming.	10 mg.
Propadrine®, phenylpropanolamine hydrochloride	0.12 Gm.
Potassium citrate	1.2 Gm.
Diluted phosphoric acid	4.5 cc.
Alcohol 5%	

Average Dose for Adults: 1 to 2 teaspoonfuls every three or four hours.

CHILDREN:
(*note:* METHAJADE *should not be administered to children under 2 years of age. In children 2 years of age or older,* METHAJADE *should be used only in cases of severe, intractable cough.*)
Two years: ¼ teaspoonful not more often than every four hours.
Five years: ½ teaspoonful not more often than every four hours.
Ten years: 1 teaspoonful not more often than every four hours.

Packaging—METHAJADE is supplied in pint Spasaver® bottles and gallon bottles.
Sharp & Dohme, Philadelphia 1, Pa.

**The analgesic potency of methadone hydrochloride is—weight for weight—approximately equivalent to that of morphine. It controls cough as well as, or better than, codeine. Methadone hydrochloride is subject to the provisions of the Harrison Narcotic Act.*

METHAJADE® Antitussive

When the diagnosis is Pyelitis

First:

consider

ACCEPTED
COUNCIL ON PHARMACY AND CHEMISTRY
AMERICAN MEDICAL ASSOCIATION

to establish and maintain urinary antisepsis...

To establish and maintain urinary antisepsis, MANDELAMINE* is many times preferred because it is quickly effective against the organisms most commonly encountered in urinary-tract infections. Its exceptional freedom from untoward reactions and its wide range of antibacterial activity commend it for use as soon as the diagnosis has been made.

Urinary antisepsis is often achieved in uncomplicated pyelitis in as few as three days. Speedy recovery is thus secured in many cases without necessitating higher-cost therapy.

Other indications for MANDELAMINE are cystitis, prostatitis, pyelonephritis, nonspecific urethritis, and infections associated with urinary calculi or neurogenic bladder; also valuable for pre- and postoperative prophylaxis in urologic surgery.

Renal insufficiency is the only major contraindication to MANDELAMINE therapy.

MANDELAMINE is available in bottles of 120, 500, and 1,000 enteric-coated tablets, through all prescription pharmacies. Comprehensive literature and samples for clinical trial will be furnished to physicians on request.

NEPERA

NEPERA CHEMICAL CO., INC.
Pharmaceutical Manufacturers
NEPERA PARK, YONKERS 2, N. Y.

*MANDELAMINE is the registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.

your patient
will not tire
of taking...

TĪTRALAC

TRADEMARK

[GLYCINE AND CALCIUM CARBONATE]

an effective antacid

continuously acceptable

TĪTRALAC's "just right" mint flavor and smooth texture ensure continuous acceptance.

acts like milk

TĪTRALAC's precise proportions of glycine and calcium carbonate provide a buffering action singularly like that of whole milk.

No systemic alkalosis or acid rebound... free from acid-generating sugars. Especially useful in milk-sensitive patients or where weight gain is undesirable.

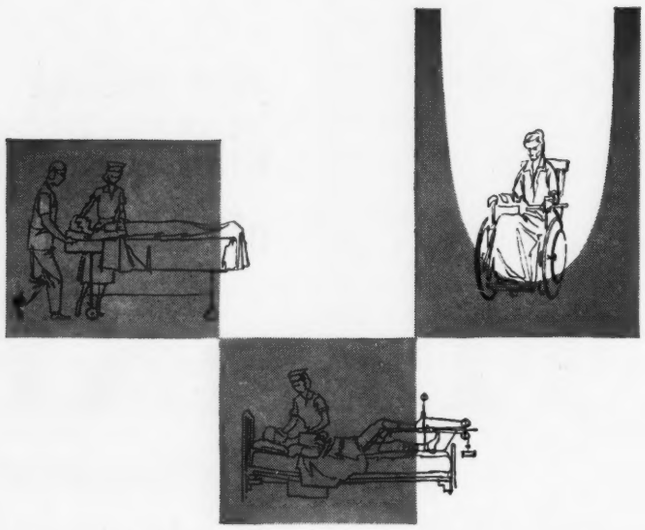
available in 3 forms

TĪTRALAC* Tablets.....Boxes of 40, bottles of 100 and 1000
TĪTRALAC Powder.....Jars of 4 oz.
TĪTRALAC Liquid..Bottles of 8 fl. oz.

*Trademark of Schenley Laboratories, Inc.
U. S. Pat. No. 2,429,596

schenley

SCHENLEY LABORATORIES, INC.
LAWRENCEBURG, INDIANA



When the need for vitamins is acute, prescribe

G E L S E A L S

THERACEBRIN

(PAN-VITAMINS, THERAPEUTIC, LILLY)

—a complete, highly potent, and scientifically balanced therapeutic vitamin combination for oral use.

1 Gelseal 'Theracebrin'

= Thiamin Chloride (Vitamin B_1), 15 mg.
Riboflavin (Vitamin B_2), 10 mg.
Pyridoxine (Vitamin B_6) Hydrochloride, 3 mg.
Pantothenic Acid (as Calcium Pantothenate), 20 mg.
Nicotinamide, 150 mg.
Ascorbic Acid (Vitamin C), 150 mg.
Distilled Tocopherols, Natural Type, 25 mg.
Vitamin A, 25,000 U.S.P. or International units
Vitamin D, 1,500 U.S.P. or International units

Detailed information and literature on Gelseals 'Theracebrin' are personally supplied by your Lilly medical service representative or may be obtained by writing to

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

The American Journal of Medicine

VOL. XI NOVEMBER, 1951 No. 5

Pennsylvania Hospital—200th Anniversary

ON VISITING THE PENNSYLVANIA HOSPITAL*

"Whose fair abode is this? Whose happy lot
Has drawn them in these peaceful shades to rest,
And hear the distant hum of busy life?
The city's noise, its clouds of smoke and dust,
Vainly invade these leafy walls that wave
On high around it, sheltering all within,
And wooing the scared bird to stay its flight
And add its note of joy to bless the scene:
The city's toils, and cares, and strifes are, sure,
Alike excluded here—Content here smiles
And reigns, and leads her vot'ries through the maze
Of flower-embroidered walks to bowers of bliss:
O! 'tis a sight to warm the heart of him
Who feels for man, and shares the joys he sees."

Francis Scott Key

THE Pennsylvania Hospital was chartered by an act of the Colonial Legislative Assembly of Pennsylvania on May 11, 1751, for "the relief of the sick poor" upon the inspiration of Dr. Thomas Bond, a prominent Philadelphia physician, and with the encouragement and dynamic public spirited assistance of Benjamin Franklin. Public support for the proposed hospital lagged until it became generally known that Franklin was behind the project. It was he who thoroughly awakened public interest by informing the public through the medium of the newspapers and by securing a grant of £2000 from the Assembly with the provision that this sum would be provided by the Provincial treasurer after a like sum had been secured by popular subscription. "This condition carried the bill through; for the members who opposed the grant, and now conceived they might have the credit of being charitable without the expense, agreed to its passage; and then, in soliciting subscriptions among the people, we urged the conditional promise of the law as an additional motive to give, since every man's donation would be doubled; thus the clause worked both ways." (Benjamin Franklin)

The house of Judge Kinsey on High Street (now Market) was used as a temporary hospital and in 1755 the cornerstone with Franklin's inscription was laid on the present site of the hospital—at Eighth and Spruce Streets. (Fig. 1.)

The hospital was well built by Samuel Rhoads, a member of the Board of Managers. In fact, some of the original buildings are still in use, notably the East Wing where legend has it that Longfellow's Evangeline and Gabriel were re-united.

The hospital began with three regularly attending physicians: Drs. Thomas Bond, Phineas Bond and Lloyd Zachary. This was

* Poems of the late Francis S. Key, Esq., author of "The Star Spangled Banner." With an introductory Letter by Chief Justice Taney. New York, 1857.

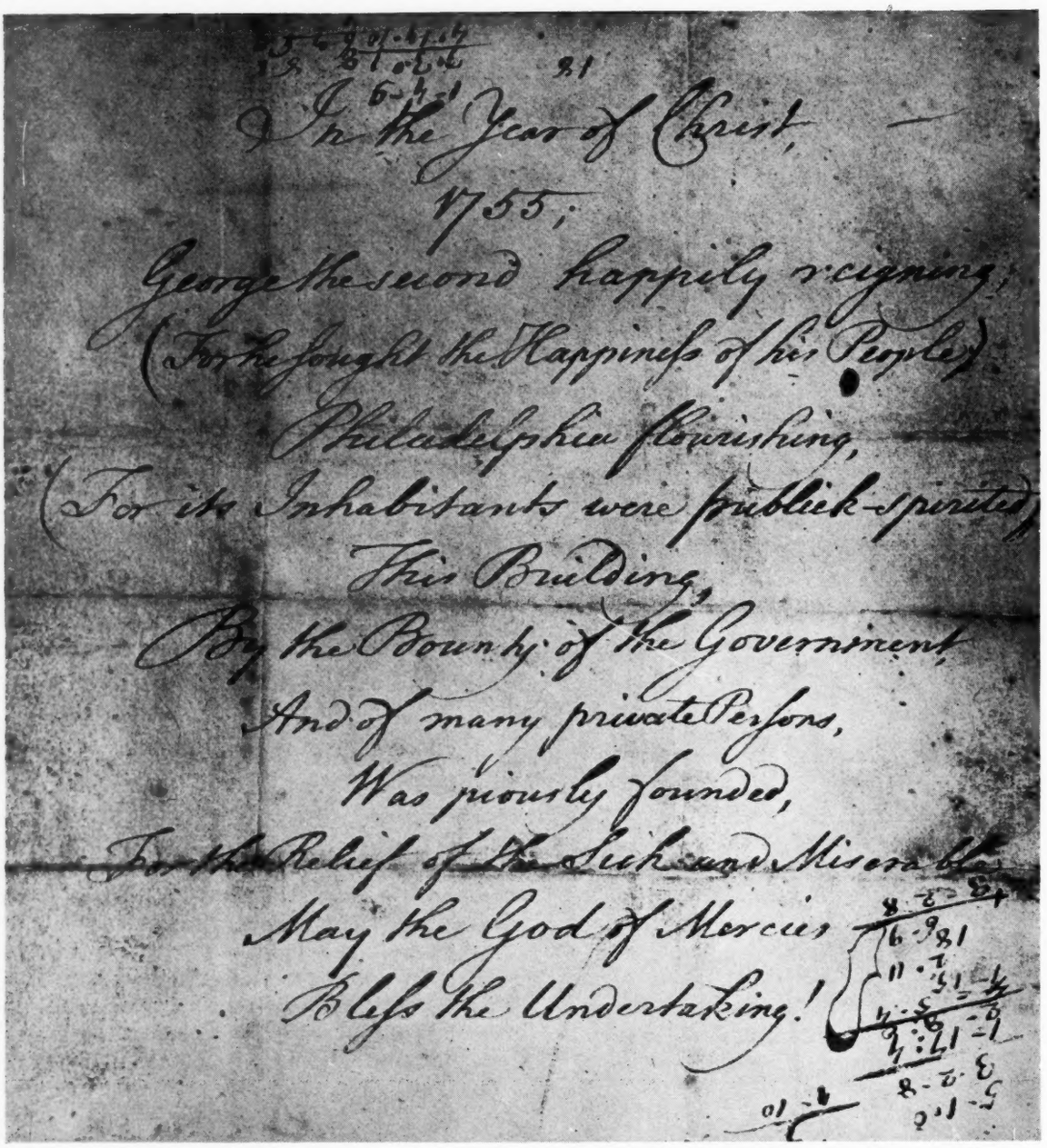

In the Year of Christ,
1755,
George the second happily reigning,
(For he sought the Happiness of his People)
Philadelphia flourishing,
(For its Inhabitants were publick-spirited)
This Building,
By the Bounty of the Government
And of many private Persons,
Was piously founded,
For the Relief of the Sick and Miserable.
May the God of Mercies
Bless the Undertaking!

FIG. 1. The manuscript of the inscription on the cornerstone of the hospital, in Benjamin Franklin's handwriting. This manuscript was purchased at an auction sale in Berlin, Germany, in 1934, through the kind efforts of Dr. A. S. W. Rosenbach. There is no information available as to how it got to Germany (Packard). There appears to have been no comment on the arithmetical error, presumably in Franklin's handwriting, in the subtraction recorded in the lower right corner. The subtraction of £3, s.2, d.8 from £5, s1., d.0, yields £1, s.18, d.4, not £1, s.17, d.4!

the first staff of the first voluntary hospital in this country. Physicians, as at present, received no remuneration and the poor were treated entirely at public expense. Treatment without cost to the patient may well have provided the inspiration for the selection, in 1754, by Thomas Bond and Benjamin Franklin, of the Good Samaritan as the official seal of the hospital. (Fig. 2.) The Out-Patient Service was inaugurated in 1752. Home Service was provided, also without charge.

Franklin served as the hospital's first clerk and the earliest minutes are in his hand. He succeeded Joshua Crosby as the second president of the Board of Managers and it was he who established the practice of collecting fines from

Board members for absences or tardiness. Fines are still levied for absences.

An extract from the minutes of one of the meetings of the Board of Managers indicates the details with which the Managers dealt, and illustrates the completeness of the records from the hospital's inception to the present.

"DIET—At a meeting of the managers the 31 of the 3 month, 1778, the stewart laid before the managers a new diet bill, which was approved, and is as follows:

"First day of the week—Breakfast—a pint of Indian grewel sweetened
Dinner—½ pound of beef, and ½ pound of potatoes or parsnips
Supper—a pint of broth

"2nd and 3rd days—Breakfast—a pint of rice grewel sweetened
Dinner—a pint of mush, or 1 lb. of rice or flour pudding, with 1 oz. of mellosses
Supper—a pint of beer each patient to have ¾ lb. of soft or ½ lb. of biscuit bread p/ diem.

"The nurse to have dinner from the matrons table every day; the rest of her diet the same as the patients, and three pounds a year added to her wages, in the place of butter, sugar and coffee."

Today's diet has more generous allowances of protein and vitamins but beer has disappeared from the menu!

The hospital, as it appears in the Hulet print (Fig. 3) from the engraving made sometime between 1756 and 1760, was used by the British for military purposes during the Revolutionary War.

Clinical lectures were begun by Dr. Thomas Bond in the Pennsylvania Hospital in 1764, one year before the founding of the first medical school in this country—the College of Philadelphia (later to become the University of Pennsylvania). Charges were made to the apprentices for these lectures.

Because of the seasonal influence on disease Dr. Bond established at the hospital a meteorologic device for the recording of the weather. These were the first systematic weather records kept in this country and were often used in court proceedings when litigation concerning the weather arose.

Some of the early physicians connected with the hospital were: Philip Syng Physick, "the father of American Surgery"; Thomas Bond, who introduced ward teaching and clinical

FIG. 2. Official seal of the hospital.

lectures in the United States at the Pennsylvania Hospital; William Shippen, Jr., who established the first systematic teaching of anatomy in America; Thomas Cadwalader, whose studies of lead colic and the first description of osteogenesis imperfecta are among his claims to fame; Caspar Wistar, famous teacher of anatomy and credited with the first medical textbook in this country; Benjamin Rush, "The American Sydenham" and the greatest historical figure in American medicine according to Welch, and "the father of psychological medicine"; John Morgan, founder of the first medical school in the United States; and Thomas Story Kirkbride, pioneer in the care of the mentally ill.

A separate building for the care of the mentally ill was erected on a farm in West Philadelphia in 1841 and was under the care of Dr. Thomas Story Kirkbride. The department is still referred to as "Kirkbride's."

The nation's first Medical Library was begun in this hospital when a book on Experimental History of the Materia Medica, written by William Lewis, F.R.S., was donated by that ever generous friend of the hospital, Dr. John Fothergill, of London, in 1762. The present library, a long room with a lofty ceiling, has served since 1796 to house the extremely valuable

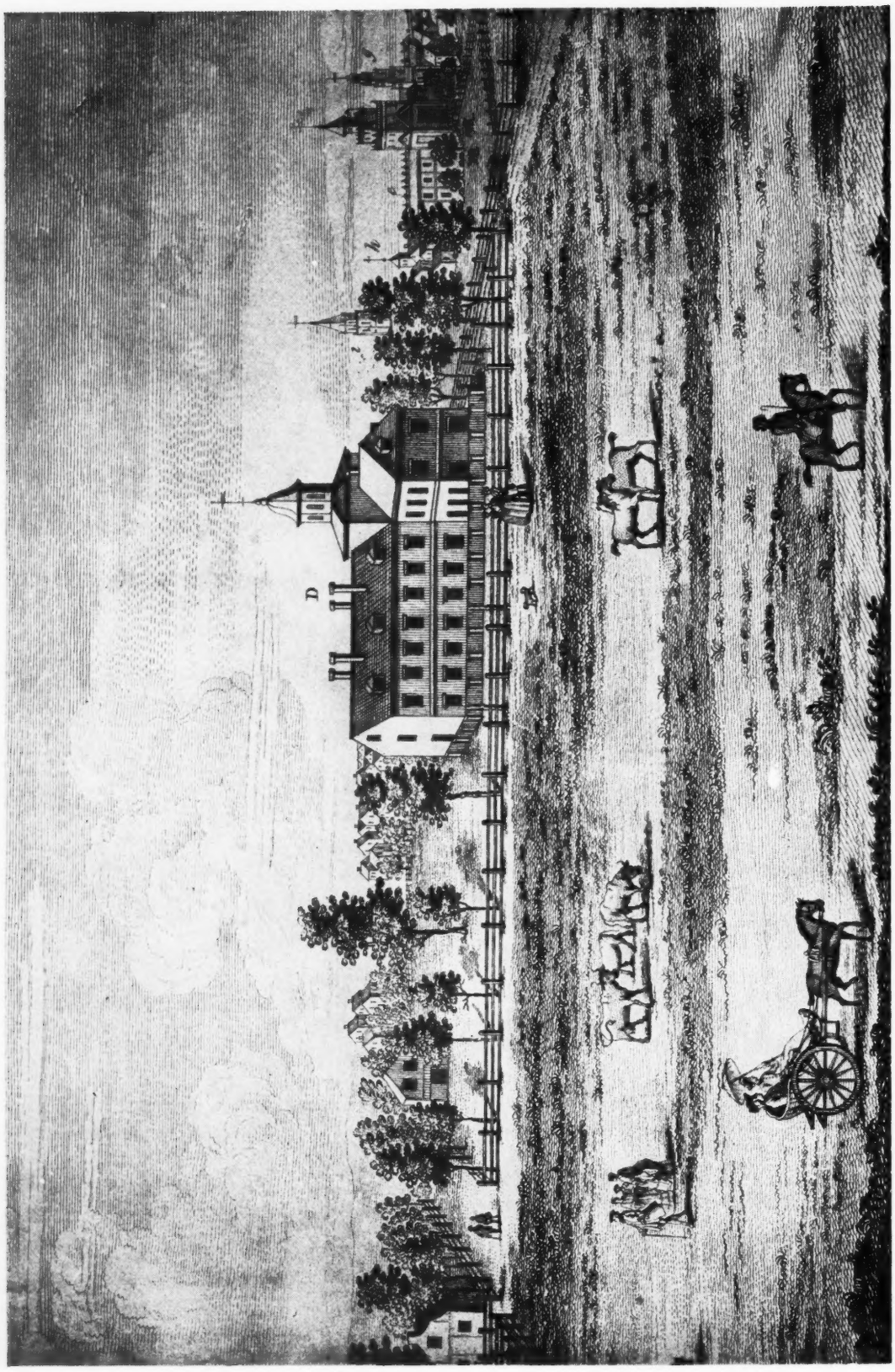


FIG. 3. The Hulett engraving is the earliest known engraving of the Pennsylvania Hospital. The hospital is building lettered D. This is the original wing of the permanent hospital. Exact date of engraving is not known. Hulet worked between 1750 and 1760.

collection of medical books, except from 1824 to 1830, when it was used as a Lying-In Ward. With the addition of large collections of books from the estates of Dr. Lloyd Zachary and Benjamin Morris and others purchased with fees collected from students attending courses at the hospital, the Library grew rapidly.

In this hospital is the nation's first clinical amphitheatre built in 1804. Professionally also, as might justly be expected, the hospital has an imposing list of "Firsts" which punctuate the history of medicine in this country.

The Training School for Nurses was opened in 1877 and one for men in 1914.

An ambulance service was established in 1877 "for the prompt and easy conveyance of cases of recent accident to the hospital from any part of the city or its vicinity and arrangements have been made, by means of telegraph communication, to obtain early information of such cases so that no time may be lost in having them admitted to our wards." A horse thought to be well suited to the ambulance service was secured without expense to the hospital. The horse drawn ambulance was abandoned in 1912 in favor of "the Motor Ambulance."

The activities of the Pennsylvania Hospital continue to revolve about the care of the patient; and in order that this care be maintained at a high standard, *clinical teaching* continues as an important function, with students coming from the Jefferson Medical College and from the University of Pennsylvania. *Clinical research*, considered an essential to the welfare of the patient, is being actively pursued. The plethora of applications annually for internship and residency training indicates that this hospital has maintained its standing with its sister institutions in the progress of American medicine.

To aid practitioners in solving obscure clinical problems the Benjamin Franklin Clinic of the Pennsylvania Hospital was established in 1948. In order to fulfill completely the motives for this clinic patients are received only upon referral from physicians. The Clinic is a co-operative diagnostic and preventive medical center conducted by a group of the Pennsylvania Hospital Staff physicians. A patient undergoes a complete diagnostic survey by respective specialists for one all-inclusive fee.

The present active staff of the Pennsylvania Hospital comprises 225 members of whom more than 190 are American Board qualified specialists, an indication that the need for specialization has been fully appreciated.

The history of the Pennsylvania Hospital has been brought up-to-date in a complete manner in several, but notably in three, publications:

1754—Benjamin Franklin presented a manuscript, "Some Account of the Pennsylvania Hospital, From its First Rise to the Beginning of the Fifth Month Called May, 1754." Fifteen hundred copies were published in Franklin's printing plant.

1895—Dr. Thomas Morton published in book form—575 pages—the "History of the Pennsylvania Hospital, 1751–1895."

1938—Dr. Francis R. Packard compiled and published in a book of some 133 pages, "Some Account of The Pennsylvania Hospital from 1751 to 1938."

In this year (1951) we observe the 200th Anniversary of this national shrine. As stated in an address by Mr. John N. Hatfield (present Administrator of the Hospital), "We are celebrating the founding of the voluntary hospital system of this country, a system that characterizes the American way of life as our founders meant it to be; a system that is emblematic of the freedom, the self-initiative and the faith found still to be inherent in us and in the rank and file of our fellow countrymen."

The Pennsylvania Hospital has weathered the vicissitudes of 200 years. On the occasion of her 200th Anniversary we do honor to her and, with a faith born of history, we see her going forward into her third century upholding and extending with dignity the spirit and the esprit de corps which pervades her halls, and the national and international reputation she has justly earned.

It is difficult for those of us whose good fortune it is to constitute the present staff of the Pennsylvania Hospital to express adequately our great appreciation to sister institutions, editors, teachers, colleagues, and all others who have, without stint, aided to make our Anniversary Year a great year. It is appropriate also to express our gratitude to those leaders of our profession who contributed papers at the scientific meetings at The Pennsylvania Hospital in connection with this celebration.

GARFIELD G. DUNCAN, M.D.
Pennsylvania Hospital, Philadelphia

Days at the Pennsylvania Hospital during Its First Century

EDWARD B. KRUMBHAAR, M.D., PH.D.
Philadelphia, Pennsylvania

WHEN this hospital was first built in 1755 in the outskirts of the small town of about 20,000 inhabitants, it was approached through the open fields by an oblique foot path. Only some of the main streets of Penn's plan had been cut through, and even in Hulett's engraving of the "House of Employment, Alms House and Pennsylvania Hospital" (ca. 1760), 8th Street alone is visible. The center of the city was then about 3rd Street, and all streets were unpaved, and unlit after dark. When the present site was under consideration, the chief objection was that it was in the country and far from the center of the city. Eventually, however, it was obtained for £500 (the equivalent then of about $1200 in terms of our dollar before devaluation).

I wish space permitted a description of the several steps that led to the founding of the hospital: Dr. Thomas Bond's original suggestion, Franklin's support, his petition to the Legislature, the shrewd condition that he inserted in the Bill of Incorporation disarming legislative opposition and at the same time stimulating private subscription. This method of provocative initial donations, by the way, is quite worthy of modern larger givers and may possibly have been the source of their inspiration. These and other details, such as the Minutes of the Organization Meeting of the Contributors, May 5, 1751, in Franklin's handwriting, the names of the first Board of Managers and the early members of the staff, etc., are all to be found in T. G. Morton's voluminous history (1895), and several have been assembled in a commemorative booklet for distribution at the present celebration. Franklin was the first clerk of the Board. Upon the death of Joshua Crosby in 1755 Franklin succeeded him as President until 1757, when he resigned to go as Provincial Agent to England. In the old library (the second story center of the old building), you will see the original records of these historic items, also the original chairs, which each of the twelve Managers agreed to supply, and other memorabilia of the Hospital collected there. You will also see a booklet of fines for Managers who were late or absent from meetings, a system proposed by Franklin, to which he proved the chief contributor on account, no doubt, of his many activities elsewhere.

Realizing that the choice and erection of an adequate hospital would take years, the Managers first looked for suitable temporary quarters which were found in (the later) Chief Justice Kinsey's house, No. 172 High Street (i.e., West of 5th Street on the south side of Market). We know very little about the hospital routine during these preliminary years. I have not been able to find any picture of the Kinsey House or other details, except that its garden extended west almost to 6th Street. Presumably the few patients could be adequately cared for by the small staff of three physicians, with the help of Elizabeth Gardner, matron from 1751 to 1760, and a few servants.

The first physicians to the hospital, Thomas Bond, Phineas Bond and Lloyd Zachary, were elected by the Board of Managers on October 23, 1751, with Thos. Graeme, Thos. Cadwalader, John Redman and S. P. Moore, as consultants. All these but the last named had studied medicine abroad. Objections as to the cost of paying the visiting physicians were met by their volunteering to serve for three years without pay, supplying their own medicines as well. The close supervision that the Managers have always exercised is illustrated in their resolution that anyone wishing to practice in the Hospital would first have to demonstrate their ability in surgery to the Board and its invited guests. Morton, however, thinks that this was never carried into effect.

Two patients were admitted on February 10, 1752: Margaret Sherlock, the first to be admitted was the first to be discharged cured soon

thereafter; Hannah Shines, the first lunatic patient, was admitted on the poor list. From the beginning the morbid curiosity of the citizens of those days to gaze at or even torment the unfortunate crazy people was a source of increasing trouble and a factor in hastening the selection and construction of the new hospital. It may at first seem surprising that this building was designed by Samuel Rhoads, one of the Managers; but professional architects were not to be had in the Colonies of those days and the builders doubtless were more experienced in safeguarding against stresses and strains. The result was not only an excellent specimen of colonial architecture—Joseph Pennell thought the main hall with its double staircase one of the best examples in the country—but also was sufficiently well adapted and flexible to be of practical use today, with but few changes. The cornerstone, with Franklin's famous inscription, was laid on May 28, 1755. The Managers, the staff, which now included William Shippen in the place of Lloyd Zachary (deceased), and many contributors and other citizens marched in a body from the temporary hospital to the new site "where a large crowd had assembled, including the children from the public schools."

The first "day" of my title that I shall consider was December 17, 1756, when all the patients, probably not over twenty-five, were moved into the completed east wing of the present original building. From the annually prepared lists of cases, we can assume that almost half of these (ten of twenty-seven remaining in the hospital on April 26, 1768) were "lunaticks," the largest number of admissions being for "scorbutick and scrophulous disorders," lunacy, ulcers with caries, dropsy, flux, and a dozen or two more in decreasing frequency. Cancer was one of the rarest, "anneurism" mentioned but once and syphilis not at all. Ague was about as common as rheumatism. While wondering if "gutta serena" meant amaurosis and if "imposthume" meant abscess, as they did to Dunglison a century later, we must not forget that at that time, and for at least another half century for that matter, illnesses were named and classified mostly on the basis of symptoms and that it was the names and not the diseases that changed.

The patients were distributed in the long wards running east and west (the shaft of the T, so to speak). The lunaticks, as before, were in the basement but in special cells that were much cleaner, drier and better ventilated than before. The male sick were on the first floor, the women on the second. One entered on the 8th Street front as now into a hall which (in 1787 at least) led into apartments for the nurses, cooks and general help at either end. On the second floor were the library which, as now, also served as the Managers' room, a drug room, and at the other end the apartments of the physicians. The museum was on the third floor.

Living facilities were of the simplest but about the same as in the world outside. Heating was by wood fires only, illumination by candle light, ventilation practically restricted to opening windows, no running water and therefore no bathtubs in the present sense, the offensive chamber-pot was only beginning to be replaced by the "water-closed pot." Each bed could be isolated at will by curtains, as in the large London hospitals, a humane custom that lapsed and was only reintroduced in the present generation.

The diet was plain but nutritious, to which delicacies and wines could be added as the occasion arose but only on the physician's prescription. A contemporary sample list for the week hangs framed in the Library, though probably certain items were left out, as taken for granted. Extras "such as tea, sugar, coffee, chocolate, wines or spirits, they provide at their own expence" (sic). By 1830 a sample dinner included beef, veal, mutton or pork (usually of two kinds), boiled or roasted, with a variety of vegetables (some from the hospital's own garden); puddings, pies, or fruits in season—apples, melons, peaches, etc., for dessert; bread at pleasure.

The assistant staff of seventeen men and twenty-four women included a gardener, baker, ostler, cowkeeper, fourteen nurses and twelve attendants for the insane of both sexes.

Admissions grew steadily each year from the beginning up to 437 in 1774. According to Packard in 1763 "there had constantly been upwards of 100 patients in the house for some time." Admissions decreased during the Revolution but afterward increased slowly up to 248 in 1794. How small this seems compared to the 856 beds and 50,443 admissions in today's hospital group!

Conditions demanded more space. A successful appeal to the Legislature together with private subscriptions permitted the erection of the west wing (1796) and a few years later of

the central portion, as originally planned by Samuel Rhoads. The racial percentages of the patients is interesting. In Malin's survey of 1831, of 5,613 patients admitted over six years, about 60 per cent were Americans, 28 per cent Irish, 5 per cent English, 3 per cent German and all the rest 4 per cent.

From its beginning the contribution of the hospital to the progress of medical education has been a notable one. Dr. William Shippen, Jr., newly returned from his studies at Edinburgh, had given public lectures on anatomy and obstetrics at home, May, 1762. Shortly after, the celebrated Fothergill crayons and casts arrived, important milestones in American medical education that are still to be seen in the library, together with Fothergill's suggestion that Shippen use them in a course of lectures. Incidentally, he also suggested that Shippen would "soon be followed by an able assistant, Dr. Morgan" and that the two with suitable assistance "will be able to erect a school of physic among you"—an interesting contribution to the discussion of who should be recognized as the founder of our first medical school three years later. The next spring Shippen was authorized by the Managers to lecture on the "curious anatomical plates and casts," in the Hospital Museum, an admission charge of one dollar being given for the benefit of the hospital—pupils to pay a pistole each. The first of these demonstrations could well be one of my "days," if its date were known.

The Library, another important tool in medical education, may be said also to owe its origin to Fothergill, who presented in 1762 "An Experimental History of the Materia Medica" by William Lewis, F.R.S. Gifts and purchases in London, with the help of Franklin, Fothergill and Lettsom, stimulated rapid growth, making it for many years the biggest and best medical library in the city, until in the 1870's when it was outstripped by that of the College of Physicians. I must add here the generous action of the Managers in giving to the College at Dr. Packard's suggestion, all of its rare old books which the College did not have represented in their own collection.

"Clynical" teaching was given at the hospital from its start—first to the apprentices of the staff physicians. Benjamin Rush, for instance, during his six years apprenticeship with John Redman accompanied his master on his visits to the Pennsylvania Hospital to dress wounds and assist generally, also attending Shippen's lectures. Soon others were allowed to make the ward rounds and before long in such numbers that the Staff recommended that those who passed the scrutiny of the Manager and Doctors in attendance were to pay 6 pistoles, which the Staff proposed "to be applied to the founding of a medical library." After one year of successful instruction the students were to be given certificates signed by Managers and Staff.

Another "day" that we must select is November 26, 1766, on which the Hospital had the honor of instituting the first regular course of clinical lectures in America, an occurrence of prime importance in American medical education. The introductory lecture on this November day, an essay by Dr. Thomas Bond on "The Utility of Clinical Lectures," was read to the Managers and Staff. Though it was only two months after Morgan's and Shippen's introductory lectures in the newly founded medical school of the College of Philadelphia, the connection between them is not clear. Bond to be sure was requested by the School's Trustees two years later to continue his lectures, but he seems never to have been listed on the faculty of the School and his lectures were open to all. The fees (in 1774) amounted to £5 for the series. Bond's essay, which Morton's history reprinted in full from the Manager's minutes, contains much wisdom mingled with the usual eighteenth century embellishments. He points out the need for clinical lectures to link examples found in cases in the hospital with the medical school's systematic lectures on the Theory and Practice of Physic; and, where the case ends in the death of the patient, the desirability of checking the physicians' clinical observations and diagnosis "by exposing all the Morbid parts to View. . . . the surest method of obtaining just Ideas of Disease." Bond supports these views with an account of two recent deaths in which "the state of all the Morbid Parts were predicted before they were exposed to view," quite in the style of a modern clinico-pathologic conference. Bond gave such lectures until his death in 1784 and they have been carried on by the staff to this day. It is unfortunately true that for a full century clinical instruction by practical lectures and ward rounds languished in America. All honor, then, to those who initiated in this country both of these procedures in this Hospital which has always encouraged use of its clinical material for teaching!

Morton tells of two difficulties with students

that appear in the Managers' minutes—a small number when we consider that the decorous, hardworking modern medical student is a product of the present century. In 1806 the Managers required Dr. Shippen to request the students to conduct themselves quietly and to inform them that all who were not privileged "to attend the practice of the Hospital will pay 1 dollar and get an admission ticket to Shippen's lectures in the Museum." This produced a lengthy account of grievances, signed by four students, to which the Managers replied courteously but without changing the causes for grievance. The second recorded trouble was years later, in 1869, when the Managers granted the request of the Female Medical College to admit their students to lectures at the Hospital. But when they arrived to attend the clinic, "a number of male students in attendance behaved in a very indecorous manner, by hissing before the lecturer commenced . . . and after it was over by other conduct unbecoming in any well regulated Institution" (Managers' Minutes). The difficulty was met by arranging for separate clinics for the two sexes. Eventually, when the excitement had died down after several sessions, clinical lectures to mixed classes were resumed.

Let us next visit the hospital on a day in 1787, when Benjamin Rush was due to make rounds, followed by some twenty to thirty "students in Physic." Fortunately the Rev. Manasseh Cutler, who paid a visit to the hospital on that day, has left the following account of it in his Journal:

"After we had taken a view of the Museum, we returned to the upper Hall, where several Physicians and all the young students in Physic in the City were waiting. Dr. Rush then began his examination of the sick, attended by these gentlemen, which I judged to be between twenty and thirty. We entered the upper chamber of the sick, which is the leg of the T. It is a spacious room, finely ventilated with numerous large windows on both sides. There were two tiers of beds, with their heads toward the walls, and a chair and small table between them. The room was exceedingly clean and nice, the beds and bedding appeared to be of a good quality, and the most profound silence and order were preserved upon the Doctor's entering the room. There were only women and about forty in number. Dr. Rush makes his visits with a great deal of formality. He is attended by the Physician who gives him an account of every thing material since he saw him last, and by the Apothecary of the Hospital, who mixes his prescriptions. In every case worthy of notice, he addresses the young Physicians, points out its nature, the probable tendency, and the reason for the mode of treatment which he pursues. On this occasion the Doctor was particularly attentive and complaisant to me, and seemed to consider me as a Physician.

"From this room we went to the next below it, which is in every respect similar. It is appropriated to the men. He began, as before, on one side, and went around the room. Every patient is on his own bed or chair. Most of the cases were chronic, many of them swellings and ulcerations, and some of them very singular; but I have not time to describe them. Their dressings were all ready to be taken off and exposed to view the instant the Doctor came to them. These disorders he imputed to their drinking spirituous liquors, and did not fail to remind them of it. He told me the greater proportion of his patients in the city were similar cases and originated from the same cause. There were between forty and fifty in this room."

Let us now pay another visit on a Sunday, when visitors were most numerous, to see the mentally disordered, who played a passive role in some of the most significant contributions of the hospital to medical progress. Even in the High Street hospital, in Judge Kinsey's house, the condition of the insane gave concern. We find them in the damp cellar with poor lighting, and already some had died from "consumption." As was the universal custom, the excited cases of so-called "Phrenzy" were chained to the wall. In the old library you can see framed a bill dated March 7, 1752, from one John Cresson, blacksmith, for sturdy handcuffs, rings, chains, "madd jackets," etc. In the new Pine Street Hospital living conditions were somewhat better. The cells had raised plank floors and were better lit, though no fires were possible. Spectators, impelled to look at the lunatics by a curiosity that existed on both sides of the Atlantic, continued to be troublesome as may be seen in a number of the Managers' resolutions:—a "pallisade" fence in front of the cell windows proving insufficient, a "hatch door" was erected through which "persons who came out of curiosity . . . should pay at least a groat to enter." Eventually not more than two visitors at a time were allowed to go into the cells and then with the cell keeper and were not suffered to speak to the patients (1784); by 1793 all curiosity seekers

were excluded. Hogarth's view of a ward in Bedlam (Bethlehem Hospital) gives a frank, if perhaps exaggerated, picture on a much larger scale. In the Cutler Journal, already referred to, his visit to them is described as follows:

"Their cells are in the lower story, which is partly underground. These cells are about ten feet square, made as strong as a prison. On the back part is a long entry, from which a door opens into each of them; in each door is a hole, large enough to give them food, etc., which is closed with a little door secured with strong bolts. On the opposite side is a window, and large iron grates within to prevent their breaking the glass. They can be darkened at pleasure. Here were both men and women, between twenty and thirty in number. Some of them have beds, most of them clean straw. Some of them were extremely fierce and raving, nearly or quite naked; some singing and dancing; some in despair; some were dumb and would not open their mouths; other incessantly talking. It was curious indeed to see in what different strains their distraction raged. This would have been a melancholy scene indeed, had it not been that there was every possible relief afforded them in the power of man. Everything about them, notwithstanding the labor and trouble it must have required, was neat and clean. From this distressing view of what human nature is liable to, and the pleasing evidence of what humanity and benevolence can do, we returned to the room where the Directors were. . . . Such is the elegance of these buildings, the care and attention to the sick, the spacious and clean apartments, and the perfect order in every thing, that it seemed more like a palace than a hospital, and one would almost be tempted to be sick, if they could be so well provided for."

Their stay in hospital must have been a long one, as the records show that the Hospital cared for only twenty-four lunatics during 1783; twenty years later (1804) the number was doubled to forty-nine.

The Reverend's optimistic picture was not altogether shared by the patients, who frequently "eloped" and in larger numbers than from other Departments of the hospital. In 1758 stronger bars had to be placed in the windows. Nor was Cutler's complacency shared by Rush, who never ceased to bombard the Managers with memorials suggesting improvements in handling these unhappy people. It must be remembered that at that period there were no lunatic laws and the Managers, authorized by their charter to make all necessary rules, admitted suitable patients at the request of the physician, after which the word of the staff physician, or death, or elopement, provided the only means of escape.

The most solid and praiseworthy of the many sided Rush's achievements were his efforts to improve the condition of the insane; even his fierce looking "Tranquilisator" was designed to quiet the patient by enforcing muscular rest. (We all know how an animal that has to be restrained will be quieter and struggle less if he is firmly held than if he thinks he can break loose.) Rush was a pioneer in this country of the attitude exemplified by Tuke in England and Pinel in France that the insane were suffering from a disease and were not merely wild animals to be confined as a protection to the public. He also was one of the earliest of his time to appreciate the advantages of occupational therapy; his letters to the Managers in 1796 and again in 1810 proposed various forms of labor and amusements involving exercise. Also it should be remembered that the Managers soon after the Hospital started provided spinning wheels and carded wool and flax to occupy the patients. Rush's matured views are set forth in more detail in his Medical Enquiries and observations on Diseases of the Mind (1812). As we all know, occupational therapy today plays a role in an even wider group of disorders, including the neuropsychoses, a field in which the Hospital's Institute has also played a pioneering role in this country.

Entering the nineteenth century, we find the staff increased to three physicians (Parke, Rush and B. S. Barton) and three surgeons (Shippen, Wistar and Physick). The two medical student apprentices were Lee and James Hutchinson, Jr., whose father had died during the yellow fever epidemic of 1793. These were replaced by graduate Resident Physicians in 1824, the first two being Casper Wistar, Jr. and Caspar Morris. At the end of the Hospital's first century the staff had been increased to eight; but the number of Resident Physicians remained at two.

The contributions to medical progress by the Staff of this period had become too numerous to mention here. Among them were such items as Rush's original observation of dengue (break bone fever); the relation of bad teeth to focal infection; Physick's removal of over a thousand bladder stones from Chief Justice Marshall in

the latter's seventy-fifth year; J. C. Otto's elucidation of the inheritance of hemophilia; J. K. Mitchell's essay on the origin of malarious fever, one of the first briefs in this country for the parasitic nature of infectious diseases; W. W. Gerhard's differentiation of typhus and typhoid fevers; John Rhea Barton's figure-of-eight bandage, which is still in use. Several of these, to be sure, were produced before or after the individual's active connection with the hospital.

We might pick a "day" to see Dr. Physick, admittedly the greatest American surgeon of his day, using absorbable catgut or the flexible catheter of his invention, or working on one of his many cataract removals or the repair of a double hare-lip, the "cancerous eye" with a drawing inserted in the record, or removing the 7 pound tumor on the cheek of James Hayes, extirpated successfully in 1805 but diagnosed as a mixed tumor of the parotid by Dr. John R. Paul 118 years later. It has been remarked that this can assuredly be regarded as the longest delay on record in the form of a pathologist's report without a complaint from the surgeon. Another of Dr. Physick's inventions that had to wait only twenty-eight years for the completion of the story was the seton. To cope with the almost 100% failure of ununited fractures of the limbs, he introduced setons through the bone at the site of fracture, in order that the long-continued irritation would stimulate bony union. In one such case in which good union had been secured the patient came to autopsy twenty-eight years later. When the bone was dissected, a hole was found in the middle of the bony callus through which the seton had passed.

I have trespassed far too much on your time; but if I have been able to bring some of the life of the hospital in its early days before you, I hope that this will be a sufficient excuse.

Reprints of Historical Interest

An Account of the Bilious Remitting Fever,

*As It Appeared in Philadelphia, in the Summer and Autumn of the Year 1780**

BENJAMIN RUSH, M.D.†
Philadelphia, Pennsylvania

BEFORE I proceed to describe this fever, it will be necessary to give a short account of the weather, and of the diseases which preceded its appearance.

The spring of 1780 was dry and cool. A catarrh appeared among children between one year and seven years of age. It was accompanied by a defluxion from the eyes and nose, and by a cough and dyspnœa, resembling, in some instances, the cynanche trachealis, and in others a peripneumony. In some cases it was complicated with the symptoms of a bilious remitting and intermitting fever. The exacerbations of this fever were always attended with dyspnœa and cough. A few patients expectorated blood. Some had swellings behind their ears, and others were affected with small ulcers in the throat. I met with only one case of this fever in which the pulse indicated bleeding. The rest yielded in a few days to emetics, blisters, and the bark, assisted by the usual more simple remedies in such diseases.

An intermittent prevailed among adults in the month of May.

July and August were uncommonly warm. The mercury stood on the 6th of August at 94½, on the 15th of the same month at 95°, and for several days afterwards at 90°. Many labouring people perished during this month by the heat, and by drinking, not only cold water but cold liquors of several kinds, while they were under the violent impressions of the heat.

The vomiting and purging prevailed universally, during these two warm months, among the children, and with uncommon degrees of mortality. Children from one year to eight and nine years old were likewise very generally affected by blotches and little boils, especially in their faces. An eruption on the skin, called by the common people the prickly heat, was very common at this time among persons of all ages. The winds during these months blew chiefly from the south, and southwest. Of course they passed over the land which lies between the city, and the conflux of the rivers Delaware and Schuylkill, the peculiar situation of which, at that time, has been already described.

The dock, and the streets of Philadelphia, supplied the winds at this season, likewise, with a portion of their unwholesome exhalations.

The moschetoes were uncommonly numerous during the autumn. A certain sign (says Dr. Lind) of an unwholesome atmosphere.

The remitting fever made its first appearance

* Reprinted from Medical Inquiries and Observations. By BENJAMIN RUSH. Vol. II, 3rd ed. Philadelphia, 1809. Mathew Carey, Hopkins and Earle, Johnson and Warner, Kimber and Conrad, Bradford and Inskeep, Thomas and William Bradford, Benjamin and Thomas Kite, and Bennett and Walton.

† The 1780 epidemic of "bilious remitting fever" occurring in Philadelphia and reported by Benjamin Rush would, in present day terminology, be reported as dengue. This was not the first but was probably the best description of this disease in which several features are of special interest. The term "breakbone fever" given to the disease by the suffering populace of Philadelphia was recorded and continues to be synonymous with dengue. Also, the season of the year, weather conditions and "uncommonly numerous" mosquitoes, in some manner not clear in 1780, combined to provide the suitable setting or "unwholesome atmosphere" for an epidemic of this disease.

Rush's description of the evolution of the epidemic, the clinical attack with the saddle back, "remitting" fever, and the rash are classic. Most of his patients were not bled but none escaped the sweating and purging technic. In contrast today, prevention by control of the mosquito of the genus Aedes represents the greatest advance in coping with this viral disease in the 171 intervening years. Today we permit the patient to retain his hematologic and water balance defenses but have substituted nothing more specific than good nursing care and "tincture of time" for patients suffering from this particularly distressing malady. (G.G.D.)

in July and August, but its symptoms were so mild, and its extent so confined, that it excited no apprehensions of its subsequent more general prevalence throughout the city.

On the 19th of August the air became suddenly very cool. Many hundred people in the city complained, the next day, of different degrees of indisposition, from a sense of lassitude to a fever of the remitting type. This was the signal of the epidemic. The weather continued cool during the remaining part of the month, and during the whole month of September. From the exposure of the district of Southwark (which is often distinguished by the name of the *Hill*) to the southwest winds, the fever made its first appearance in that appendage of the city. Scarcely a family, and, in many families, scarcely a member of them, escaped it. From the Hill it gradually travelled along the second street from the Delaware, improperly called Front-street. For a while it was confined to this street only, after it entered the city, and hence it was called by some people the *Front-street fever*. It gradually spread through other parts of the city, but with very different degrees of violence. It prevailed but little in the Northern Liberties. It was scarcely known beyond Fourth-street from the Delaware. Intemperance in eating or drinking, riding in the sun or rain, watching, fatigue, or even a fright, but more frequently cold, all served to excite the seeds of this fever into action, wherever they existed.

All ages and both sexes were affected by this fever. Seven of the practitioners of physics were confined by it nearly at the same time. The city, during the prevalence of the fever, was filled with an unusual number of strangers, many of whom, particularly the Friends (whose yearly meeting was held in the month of September), were affected by it. No other febrile disease was observed during this time in the city.

This fever generally came on with rigour, but seldom with a regular chilly fit, and often without any sensation of cold. In some persons it was introduced by a slight sore throat, and in others by a hoarseness which was mistaken for a common cold. A giddiness in the head was the forerunner of the disease in some people. This giddiness attacked so suddenly, as to produce, in several instances, a faintness, and even symptoms of apoplexy. It was remarkable that all those persons who were affected in this violent manner, recovered in two or three days.

I met with one instance of this fever attacking with coma, and another with convulsions, and with many instances, in which it was introduced by a delirium.

The pains, which accompanied this fever were exquisitely severe in the head, back, and limbs. The pains in the head were sometimes in the back parts of it, and at other times they occupied only the eyeballs. In some people, the pains were so acute in their backs and hips, that they could not lie in bed. In others, the pains affected the neck and arms, so as to produce in some instance a difficulty of moving the fingers of the right hand. They all complained more or less of a soreness in the seats of these pains, particularly when they occupied the head and eyeballs. A few complained of their flesh being sore to the touch, in every part of the body. From these circumstances, the disease was sometimes believed to be a rheumatism; but its more general name among all classes of people was, the *break-bone fever*.

I met with one case of pain in the back, and another of an acute ear-ach, both of which returned periodically every night, and without any fever.

A nausea universally, and in some instances a vomiting, accompanied by a disagreeable taste in the mouth, attended this fever. The bowels were in most cases, regular, except where the disease fell with its whole force upon them, producing a dysentery.

The tongue was generally moist, and tinctured of a yellow colour.

The urine was high coloured, and in its usual quantity in fevers.

The skin was generally moist, especially where the disease terminated on the third or fourth day.

The pulse was quick and full, but never hard, in a single patient that came under my care, till the 28th of September.

It was remarkable, that little, and, in some instances, no thirst attended this fever.

A screatus, or constant hawking and spitting, attended in many cases through the whole disease, and was a favourable symptom.

There were generally remissions in this fever every morning, and sometimes in the evening. The exacerbations were more severe every other day, and two exacerbations were often observed in one day.

A rash often appeared on the third and fourth days, which proved favourable. This rash was accompanied, in some cases, by a burning in the palms of the hands and soles of the feet. Many

people at this time, who were not confined to their beds, and some, who had no fever, had an efflorescence on their skins.

In several persons the force of the disease seemed to fall upon the face, producing swellings under the jaw and in the ears, which in some instances terminated in abscesses.

When the fever did not terminate on the third or fourth day, it frequently ran on to the eleventh, fourteenth, and even twentieth days, assuming in its progress, according to its duration, the usual symptoms of the typhus gravior, or mitior, of Doctor Cullen. In some cases, the discharge of a few spoons-full of blood from the nose accompanied a solution of the fever on the third or fourth day; while in others, a profuse hemorrhage from the nose, mouth, and bowels, on the tenth and eleventh days, preceded a fatal issue of the disease.

Several cases came under my care, in which the fever was succeeded by a jaundice.

The disease terminated in some cases without sweating or sediment in the urine; nor did I observe such patients more disposed to relapse than others provided they took a sufficient quantity of the bark.

About the beginning of October the weather became cool, accompanied by rain and an easterly wind. This cool and wet weather continued for four days. The mercury in the thermometer fell to 60°, and fires became agreeable. From this time the fever evidently declined, or was accompanied by inflammatory symptoms. On the 16th of October, I met with a case of inflammatory angina; and on the next day I visited a patient who had a complication of the bilious fever with a pleurisy, and whose blood discovered strong marks of the presence of the inflammatory diathesis. His stools were of a green and black colour. On the third day of his disease a rash appeared on his skin, and on the fourth, in consequence of a second bleeding, his fever terminated with the common symptoms of a crisis.

During the latter end of October, and the first weeks in November, the mercury in the thermometer fluctuated between 50° and 60°. Pleurisies and inflammatory diseases of all kinds now made their appearance. They were more numerous and more acute, than in this stage of the autumn, in former years. I met with one case of pleurisy in November, which did not yield to less than four plentiful bleedings.

I shall now add a short account of the METHOD I pursued in the treatment of this fever.

I generally began by giving a gentle vomit of tartar emetic. This medicine, if given while the fever was in its forming state, frequently produced an immediate cure; and if given after its formation, on the *first* day, seldom failed of producing a crisis on the third or fourth day. The vomit always discharged more or less bile. If a nausea, or an ineffectual attempt to vomit continued after the exhibition of the tartar emetic, I gave a second dose of it with the happiest effects.

If the vomit failed of opening the bowels, I gave gentle doses of salts and cream of tartar,* or of the butter-nut pill,† so as to procure two or three plentiful stools. The matter discharged from the bowels was of a highly bilious nature. It was sometimes so acrid as to excoriate the rectum, and so offensive, as to occasion, in some cases, sickness and faintness both in the patients and in their attendants. In every instance, the patients found relief by these evacuations, especially from the pains in the head and limbs.

In those cases, where the prejudices of the patients against an emetic, or where an advanced state of pregnancy, or a habitual predisposition to a vomiting of blood occurred, I discharged the bile entirely by means of the lenient purges that have been mentioned. In this practice I had the example of Doctor Cleghorn, who prescribed purges with great success in a fever of the same kind in Minorca, with that which has been described.‡ Doctor Lining prescribed purges with equal success in an autumnal pleurisy in South Carolina, which I take to have been a form of a bilious remittent, accompanied by an inflammatory affection of the breast.

After evacuating the contents of the stomach and bowels, I gave small doses of tartar emetic, mixed with Glauber's salt. This medicine excited a general perspiration. It likewise kept the bowels gently open, by which means the bile was discharged as fast as it was accumulated.

* I have found that cream of tartar renders the purging neutral salts less disagreeable to the taste and stomach; but accident has lately taught me, that the juice of two limes or of one lemon, with about half an ounce of loaf sugar, added to six drachms of Glauber's or Epsom salt, in half a pint of boiling water, form a mixture that is nearly as pleasant as strong beverage.

† This pill is made from an extract of a strong decoction of the inner bark of the white walnut-tree.

‡ The tertiana interposita remissione tantum of Dr. Cullen.

I constantly recommended to my patients, in this stage of the disorder, to *lie in bed.* This favoured the eruption of the rash, and the solution of the disease by perspiration. Persons who struggled against the fever by *sitting up*, or who attempted to shake it off by labour or exercise, either sunk under it, or had a slow recovery.

A clergyman of a respectable character from the country, who was attacked by the disease in the city, returned home, from a desire of being attended by his own family, and died in a few days afterwards. This is only one, of many cases, in which I have observed travelling, even in the easiest carriages, to prove fatal in fevers after they were formed, or after the first symptoms had shown themselves. The quickest and most effectual way to conquering a fever, in most cases, is, by an early submission to it.

The drinks I recommended to my patients were sage and balm teas, weak punch, lemonade, wine whey, tamarind and apple water.

The apple water should be made by pouring boiling water upon slices of raw apples. It is more lively than that which is made by pouring the water on roasted apples.

I found obvious advantages, in many cases, from the use of pediluvia every night.

In every case, I found the patients refreshed and relieved by frequent changes of their linen.

On the third or fourth day, in the forenoon, the pains in the head and back generally abated, with a sweat which was diffused over the whole body. The pulse at this time remained quick and weak. This was, however, no objection to the use of the bark, a few doses of which immediately abated its quickness, and prevented a return of the fever.

If the fever continued beyond the third or fourth day without an intermission, I always had recourse to blisters. Those which were applied to the neck, and behind the ears, produced the most immediate good effects. They seldom failed of producing an intermission in the fever, the day after they were applied. Where delirium or coma attended, I applied the blister to the neck on the *first* day of the disease. A worthy family in this city will always ascribe the life of a promising boy, of ten years old, to the early application of a blister to the neck, in this fever.

Where the fever did not yield to blisters, and assumed malignant, or typhus symptoms, I gave the medicines usually exhibited in both those states of fever.

I took notice, in the history of this fever, that it was sometimes accompanied with symptoms of a dysentery. Where this disease appeared, I prescribed lenient purges and opiates. Where these failed of success, I gave the bark in the intermissions of the pain in the bowels, and applied blisters to the wrists. The good effects of these remedies led me to conclude, that the dysentery was the febris introversa of Dr. Sydenham.

I am happy in having an opportunity, in this place, of bearing a testimony in favour of the usefulness of OPIUM in this disease, after the necessary evacuations had been made. I yielded, in prescribing it at first, to the earnest solicitations of my patients for something to give them relief from their insupportable pains, particularly when they were seated in the eyeballs and head. Its salutary effects in procuring sweat, and a remission of the fever, led me to prescribe it afterwards in almost every case, and always with the happiest effects. Those physicians enjoy but little pleasure in practising physic, who know not how much of the pain and anguish of fevers, of a certain kind, may be lessened by the udicious use of opium.

In treating of the remedies used in this disease, I have taken no notice of blood-letting. Out of several hundred patients whom I visited in this fever, I did not meet with a single case, before the 27th of September, in which the state of the pulse indicated this evacuation. It is true, the pulse was *full*, but never *hard*. I acknowledge that I was called to several patients who had been bled without the advice of a physician, who recovered afterwards on the usual days of the solution of the fever. This only can be ascribed to that disposition which Doctor Cleghorn attributes to fevers, to preserve their types under every variety of treatment, as well as constitution. But I am bound to declare further, that I heard of several cases in which bleeding was followed by a fatal termination of the disease.

In this fever relapses were very frequent, from exposure to the rain, sun, or night air, and from an excess in eating or drinking.

The convalescence from this disease was marked by a number of extraordinary symptoms, which rendered patients the subjects of medical attention for many days after the pulse became perfectly regular, and after the crisis of the disease.

A bitter taste in the mouth, accompanied by a yellow colour on the tongue, continued for near a week.

Most of those who recovered complained of nausea, and a total want of appetite. A faintness, especially upon sitting up in bed, or in a chair, followed this fever. A weakness in the knees was universal. I met with two patients, who were most sensible of this weakness in the right knee. An inflammation in one eye, and in some instances in both eyes, occurred in several patients after their recovery.

But the most remarkable symptom of the convalescence from this fever, was an uncommon dejection of the spirits. I attended two young ladies, who shed tears while they vented their complaints of their sickness and weakness. One of them very aptly proposed to me to change the name of the disease, and to call it, in its present stage, instead of the break-bone, the *break-heart fever*.

To remove these symptoms, I gave the tincture of bark and elixir of vitriol in frequent doses. I likewise recommended the plentiful use of ripe fruits; but I saw the best effects from temperate meals of oysters, and a liberal use of porter. To these was added, gentle exercise in the open air, which gradually completed the cure.

Observations on the Duties of a Physician, and the Methods of Improving Medicine

*Accommodated to the Present State of Society and Manners in the United States**

Delivered in the University of Pennsylvania, February 7, 1789, at the conclusion of a course of lectures upon chemistry and the practice of physic. Published at the request of the class.

BENJAMIN RUSH, M.D.†

Philadelphia, Pennsylvania

GENTLEMEN,

I shall conclude our course of lectures, by delivering to you a few directions for the regulation of your future conduct and studies, in the line of your profession.

I shall, *first*, suggest the most probable means of establishing yourselves in business, and of becoming acceptable to your patients, and respectable in life.

Secondly, I shall mention a few thoughts which have occurred to me on the mode to be pursued, in the further prosecution of your studies, and for the improvement of medicine.

1. Permit me, in the first place, to recommend to such of you as intend to settle in the country, to establish yourselves as early as possible upon *farms*. My reasons for this advice are as follows:

1. It will reconcile the country people to the liberality and dignity of your profession, by showing them that you assume no superiority over them from your education, and that you intend to share with them in those toils, which were imposed upon man in consequence of the loss of his innocence. This will prevent envy, and render you acceptable to your patients as men, as well as physicians.

2. By living on a farm you may serve your country, by promoting improvements in agriculture. Chemistry (which is now an important branch of medical education) and agriculture are closely allied to each other. Hence some of the most useful books upon agriculture have been written by physicians. Witness the essays of Dr. Home of Edinburgh, and of Dr. Hunter of Yorkshire, in England.

3. The business of a farm will furnish you with employment in the healthy seasons of the year, and thereby deliver you from the taedium vitae, or, what is worse, from retreating to low or improper company. Perhaps one cause of the prevalence of dram or grog drinking, with which country practitioners are sometimes charged, is owing to their having no regular or profitable business to employ them, in the intervals of their attendance upon their patients.

4. The resources of a farm will create such an independence, as will enable you to practice with more dignity, and at the same time screen you from the trouble of performing unnecessary services to your patients. It will change the nature of the obligation between you and them. While *money* is the only means of your subsistence, your patients will feel that they are the channels of your daily bread; but while your farm furnishes you with the necessaries of life, your patients will feel, more sensibly, that the obligation is on their side, for health and life.

5. The exigencies and wants of a farm, in *stock* and *labour* of all kinds, will enable you to obtain from your patients a compensation for

* Reprinted from Medical Inquiries and Observations. By BENJAMIN RUSH. Vol. 1, 3rd ed. Philadelphia, 1809. Mathew Carey, Hopkins and Earle, Johnson and Warner, Kimber and Conrad, Bradford and Inskeep, Thomas and William Bradford, Benjamin and Thomas Kite, and Bennett and Walton.

† This lecture was delivered by Benjamin Rush in his capacity as Professor of the Institutes and Practice of Medicine and of Clinical Practice in the University of Pennsylvania, not in connection with his services to the Pennsylvania Hospital. But it is an essay of such charm, grace and good sense that the Editor could not resist the temptation to include it. (A.B.G.)

your services in those articles. They all possess them, and men part with that of which money is only the sign much more readily than they do with money itself.

6. The resources of a farm will prevent your cherishing, for a moment, an impious wish for the prevalence of sickness in your neighbourhood. A healthy season will enable you to add to the produce of your farm, while the rewards of an unhealthy season will enable you to repair the inconvenience of your necessary absence from it. By these means your pursuits will be marked by that *variety* and *integrity*, in which true happiness is said to consist.

7. Let your farms be small, and let your *principal* attention be directed to grass and horticulture. These afford most amusement, require only moderate labour, and will interfere least with your duties to your profession.

II. Avoid singularities of every kind in your manners, dress, and general conduct. Sir Isaac Newton, it is said, could not be distinguished in company, by any peculiarity, from a common well-bred gentleman. Singularity, in any thing, is a substitute for such great or useful qualities as command respect; and hence we find it chiefly in little minds. The profane and indelicate combination of extravagant ideas, improperly called wit, and the formal and pompous manner, whether accompanied by a wig, a cane, or a ring, should be all avoided, as incompatible with the simplicity of science, and the real dignity of physic. There is more than one way of playing the quack. It is not necessary, for this purpose, that a man should advertise his skill, or his cures, or that he should mount a phaeton, and display his dexterity in operating to an ignorant and gaping multitude. A physician acts the same part in a different way, who assumes the character of a madman or a brute in his manners, or who conceals his fallibility by an affected gravity and taciturnity in his intercourse with his patients. Both characters, like the quack, impose upon the public. It is true, they deceive different ranks of people; but we must remember that there are two kinds of vulgar, viz. the rich and the poor; and that the rich vulgar are often upon a footing with the poor, in ignorance and credulity.

III. It has been objected to our profession, that many eminent physicians have been unfriendly to christianity. If this be true, I cannot help ascribing it in part to that neglect of public worship, with which the duties of our profession are often incompatible; for it has been justly observed, that the neglect of this religious and social duty generally produces a relaxation, either in principles or morals. Let this fact lead you, in setting out in business, to acquire such habits of punctuality in visiting your patients, as shall not interfere with acts of public homage to the Supreme Being. Dr. Gregory has observed, that a cold heart is the most frequent cause of deism. Where this occurs in a physician, it affords a presumption that he is deficient in humanity. But I cannot admit that infidelity is peculiar to our profession. On the contrary, I believe christianity places among its friends more men of extensive abilities and learning in medicine, than in any other secular employment. Stahl, Hoffman, Boerhaave, Sydenham, Haller, and Fothergill, were all christians. These enlightened physicians were considered as the ornaments of the ages in which they lived, and posterity has justly ranked them among the greatest benefactors of mankind.

IV. Permit me to recommend to you a regard to all the interests of your country. The education of a physician gives him a peculiar insight in the principles of many useful arts, and the practice of physic favours his opportunities of doing good, by diffusing knowledge of all kinds. It was in Rome, when medicine was practised only by slaves, that physicians were condemned by their profession "mutam exercere artem." But in modern times, and in free governments, they should disdain an ignoble silence upon public subjects. The American revolution has rescued physic from its former slavish rank in society. For the honour of our profession it should be recorded, that some of the most intelligent and useful characters, both in the cabinet and the field, during the late war, have been physicians. The illustrious Dr. Fothergill opposed faction and tyranny, and took the lead in all public improvements in his native country, without suffering thereby the least diminution of that reputation, or business, in which, for forty years, he flourished almost without a rival in the city of London.

V. Let me advise you, in your visits to the sick, *never* to appear in a hurry, nor to talk of indifferent matters, before you have made the necessary inquiries into the symptoms of your patient's disease.

VI. Avoid making light of any case. "Respice finem" should be the motto of every indisposition. There is scarcely a disease so trifling, that

has not, directly or indirectly, proved an outlet to human life. This consideration should make you anxious and punctual in your attendance upon every acute disease, and keep you from risking your reputation by an improper or hasty prognosis.

VII. Do not condemn, or oppose, unnecessarily, the simple prescriptions of your patients. Yield to them in matters of little consequence, but maintain an inflexible authority over them in matters that are essential to life.

VIII. Preserve, upon all occasions, a composed or cheerful countenance in the room of your patients, and inspire as much hope of a recovery as you can, consistent with truth, especially in acute diseases. The extent of the influence of the will over the human body has not yet been fully ascertained. I reject the futile pretensions of Mr. Mesmer to the cure of diseases, by what he has absurdly called animal magnetism. But I am willing to derive the same advantages from his deceptions, which the chemists have derived from the delusions of the alchemists. The facts which he has established clearly prove the influence of the imagination, and will, upon diseases. Let us avail ourselves of the handle which those faculties of the mind present to us, in the strife between life and death. I have frequently prescribed remedies of doubtful efficacy in the critical stage of acute diseases, but never till I had worked up my patients into a confidence, bordering upon certainty, of their probable good effects. The success of this measure has much oftener answered, than disappointed my expectations; and while my patients have commended the vomit, the purge, or the blister, which was prescribed, I have been disposed to attribute their recovery to the vigorous concurrence of the *will* in the action of the medicine. Does the will beget insensibility to cold, heat, hunger, and danger? Does it suspend pain, and raise the body above feeling the pangs of Indian tortures? Let us not then be surprised that it should enable the system to resolve a spasm, to open an obstruction, or to discharge an offending humour. I have only time to hint at this subject. Perhaps it would lead us, if we could trace it fully, to some very important discoveries in the cure of diseases.

IX. Permit me to advise you, in your intercourse with your patients, to attend to that principle in the human mind, which constitutes the association of ideas. A chamber, a chair, a curtain, or even a cup, all belong to the means of life or death, accordingly as they are associated with cheerful or distressing ideas, in the mind of a patient. But this principle is of more immediate application in those chronic diseases which affect the mind. Nothing can be accomplished here, till we produce a new association of ideas. For this purpose a change of place and company are absolutely necessary. But we must sometimes proceed much further. I have heard of a gentleman in South Carolina, who cured his fits of low spirits by changing his clothes. The remedy was a rational one. It produced at once a new train of ideas, and thus removed the paroxysm of his disease.

X. Make it a rule never to be angry at any thing a sick man says or does to you. Sickness often adds to the natural irritability of the temper. We are, therefore, to bear the reproaches of our patients with meekness and silence. It is folly to resent injuries at any time, but it is cowardice to resent an injury from a sick man, since, from his weakness and dependence upon us, he is unable to contend with us upon equal terms. You will find it difficult to attach your patients to you by the obligations of friendship or gratitude. You will sometimes have the mortification of being deserted by those patients, who owe most to your skill and humanity. This led Dr. Turner to advise physicians never to choose their friends from among their patients. But this advice can never be followed by a heart that has been taught to love true excellency, wherever it finds it. I would rather advise you to give the benevolent feelings of your hearts full scope, and to forget the unkind returns they will often meet with, by giving to human nature —a tear.

XI. Avoid giving a patient over in an acute disease. It is impossible to tell in such cases where life ends, and where death begins. Hundreds of patients have recovered, who have been pronounced incurable, to the great disgrace of our profession. I know that the practice of predicting danger and death, upon every occasion, is sometimes made use of by physicians, in order to enhance the credit of their prescriptions, if their patients recover, and to secure a retreat from blame, if they should die. But this mode of acting is mean and illiberal. It is not necessary that we should decide with confidence, at any time, upon the issue of a disease.

XII. A physician in sickness is always a welcome visitor in a family; hence he is often solicited to partake of the usual sign of hospitality

in this country, by taking a draught of some strong liquor, every time he enters into the house of a patient. Let me charge you to lay an early restraint upon yourselves, by refusing to yield to this practice, especially in the *forenoon*. Many physicians have been innocently led by it into habits of drunkenness. You will be in the more danger of falling into this vice, from the great fatigue and inclemency of the weather to which you will be exposed in country practice. But you have been taught that strong drink affords only a temporary relief from those evils, and that it afterwards renders the body more sensible of them.

XIII. I shall now give some directions with respect to the method of charging for your services to your patients.

When we consider the expense of a medical education, and the sacrifices a physician is obliged to make of ease, society, and even health, to his profession; and when we add to these the constant and painful anxiety which is connected with the important charge of the lives of our fellow-creatures, and, above all, the inestimable value of that blessing which is the object of his services, I hardly know how it is possible for a patient sufficiently and justly to reward his physician. But when we consider, on the other hand, that sickness deprives men of the means of acquiring money; that it increases all the expences of living; and that high charges often drive patients from regular-bred physicians to quacks; I say, when we attend to these considerations, we should make our charges as moderate as possible, and conform them to the following state of things.

Avoid measuring your services to your patients by scruples, drachms, and ounces. It is an illiberal mode of charging. On the contrary, let the number and *time* of your visits, the nature of your patient's disease, and his rank in his family or society, determine the figures in your accounts. It is certainly just, to charge more for curing an apoplexy, than an intermitting fever. It is equally just, to demand more for risking your life by visiting a patient in a contagious fever, than for curing a pleurisy. You have likewise a right to be paid for your anxiety. Charge the same services, therefore, higher, to the master or mistress of a family, or to an only son or daughter, who call forth all your feelings and industry, than to less important members of a family and of society. If a rich man demand more frequent visits than are necessary, and if he impose the restraints of keeping to hours, by calling in other physicians to consult with you upon every trifling occasion, it will be just to make him pay accordingly for it. As this mode of charging is strictly agreeable to reason and equity, it seldom fails of according with the reason and sense of equity of our patients. Accounts made out upon these principles are seldom complained of by them. I shall only remark further upon this subject, that the sooner you send in your accounts after your patients recover, the better. It is the duty of a physician to inform his patient of the amount of his obligation to him at least *once* a year. But there are times when a departure from this rule may be necessary. An unexpected misfortune in business, and a variety of other accidents, may deprive a patient of the money he had allotted to pay his physician. In this case, delicacy and humanity require, that he should not know the amount of his debt to his physician, till time had bettered his circumstances.

I shall only add, under this head, that the poor of every description should be the objects of your peculiar care. Dr. Boerhaave used to say, "they were his best patients, because God was their paymaster." The first physicians that I have known have found the poor the steps, by which they have ascended to business and reputation. Diseases among the lower class of people are generally simple, and exhibit to a physician the best cases of all epidemics, which cannot fail of adding to his ability of curing the complicated diseases of the rich and intemperate. There is an inseparable connection between a man's duty and his interest. Whenever you are called, therefore, to visit a poor patient, imagine you hear the voice of the good Samaritan sounding in your ears, "Take care of him, and I will repay thee."

I come now to the second part of this address, which was to point out the best mode to be pursued, in the further prosecution of your studies, and the improvement of medicine.

I. Give me leave to recommend to you, to open all the dead bodies you can, without doing violence to the feelings of your patients, or the prejudices of the common people. Preserve a register of the weather, and of its influence upon the vegetable productions of the year. Above all, record the epidemics of every season; their times of appearing and disappearing, and the connection of the weather with each of them. Such records, if published, will be useful to foreigners,

and a treasure to posterity. Preserve, likewise, an account of chronic cases. Record the name, age, and occupation of your patient; describe his disease accurately, and the changes produced in it by your remedies; mention the doses of every medicine you administer to him. It is impossible to tell how much improvement and facility in practice you will find from following these directions. It has been remarked, that physicians seldom remember more than the two or three last years of their practice. The records which have been mentioned will supply this deficiency of memory, especially in that advanced stage of life, when the advice of physicians is supposed to be most valuable.

II. Permit me to recommend to you further, the study of the anatomy (if I may be allowed the expression) of the human mind, commonly called metaphysics. The reciprocal influence of the body and mind upon each other can only be ascertained by an accurate knowledge of the faculties of the mind, and of their various modes of combination and action. It is the duty of physicians to assert their prerogative, and to rescue the mental science from the usurpations of schoolmen and divines. It can only be perfected by the aid and discoveries of medicine. The authors I would recommend to you upon metaphysics are, Butler, Locke, Hartley, Reid, and Beattie. These ingenious writers have cleared this sublime science of its technical rubbish, and rendered it both intelligible and useful.

III. Let me remind you, that improvement in medicine is not to be derived only from colleges and universities. Systems of physic are the productions of men of genius and learning; but those facts which constitute real knowledge are to be met with in every walk of life. Remember how many of our most useful remedies have been discovered by quacks. Do not be afraid, therefore, of conversing with them, and of profiting by their ignorance and temerity in the practice of physic. Medicine has its Pharisees, as well as religion. But the spirit of this sect is as unfriendly to the advancement of medicine, as it is to christian charity. By conversing with quacks, we may convey instruction to them, and thereby lessen the mischief they might otherwise do to society. But further. In the pursuit of medical knowledge, let me advise you to converse with nurses and old women. They will often suggest facts in the history and cure of diseases, which have escaped the most sagacious observers of nature. Even Negroes and Indians have sometimes stumbled upon discoveries in medicine. Be not ashamed to inquire into them. There is yet one more means of information in medicine which should not be neglected, and that is, to converse with persons who have recovered from indispositions without the aid of physicians. Examine the strength and exertions of nature in these cases, and mark the plain and home-made remedy to which they ascribe their recovery. I have found this to be a fruitful source of instruction, and have been led to conclude, that if every man in a city, or a district, could be called upon to relate, to persons appointed to receive and publish his narrative, an exact account of the effects of those remedies which accident or whim has suggested to him, it would furnish a very useful book in medicine. To preserve the facts thus obtained, let me advise you to record them in a book to be kept for that purpose. There is one more advantage that will probably attend the inquiries that have been mentioned; you may discover diseases, or symptoms of diseases, or even laws of the animal economy, which have no place in our systems of nosology, or in our theories of physic.

IV. Study simplicity in the preparation of your medicines. My reasons for this advice are as follows:

1. Active medicines produce the most certain effects in a simple state.

2. Medicines when mixed frequently destroy the efficiency of each other. I do not include chemical medicines alone in this remark. It applies likewise to Galenical medicines. I do not say that all these medicines are impaired by mixture, but we can only determine when they are not, by actual experiments and observations.

3. When medicines of the same class, or even of different classes, are given together, the *strongest* only produces an effect. But what are we to say to a compound of two medicines, which give exactly the same impression to the system? Probably, if we are to judge from analogy, the effect of them will be such, as would have been produced by neither in a simple state.

4. By observing simplicity in your prescriptions, you will always have the command of a greater number of medicines of the *same* class, which may be used in succession to each other, in proportion as habit renders the system insensible of their action.

5. By using medicines in a simple state, you will obtain an exact knowledge of their virtues

and doses, and thereby be able to decide upon the numerous and contradictory accounts which exist in our books, of the character of the *same* medicines.

Under this head, I cannot help adding two more directions.

1. Avoid sacrificing too much to the *taste* of your patients in the preparation of your medicines. The nature of a medicine may be wholly changed, by being mixed with sweet substances. The Author of Nature seems to have had a design in rendering medicines unpalatable. Had they been more agreeable to the taste, they would probably have yielded long ago to the unbounded appetite of man, and by becoming articles of diet, or condiments, have lost their efficacy in diseases.

2. Give as few medicines as possible in tinctures made with distilled spirits. Perhaps there are few cases, in which it is safe to exhibit medicines prepared in spirits in any other form than in *drops*. Many people have been innocently seduced into a love of strong drink, from taking large or frequent doses of bitters infused in spirits. Let not our profession be reproached, in a single instance, with adding to the calamities that have been entailed upon mankind by this dreadful species of intemperance.

v. Let me recommend to your particular attention the indigenous medicines of our country. Cultivate or prepare as many of them as possible, and endeavor to enlarge the materia medica, by exploring the untrodden fields and forests of the United States. The ipecacuanha, the Seneka and Virginia snake-roots, the Carolina pink-root, the spice-wood, the sassafras, the butter-nut, the thoroughwort, the poke, and the stramonium, are but a small part of the medical productions of America. I have no doubt but there are many hundred other plants, which now exhale invaluable medicinal virtues in the desert air. Examine, likewise, the mineral waters, which are so various in their impregnation, and so common in all parts of our country. Let not the properties of the insects of America escape your investigation. We have already discovered among some of them a fly, equal in its blistering qualities to the famous fly of Spain. Who knows but it may be reserved for America to furnish the world, from her productions, with cures for some of those diseases which now elude the power of medicine? Who knows but that, at the foot of the Allegany mountain, there blooms a flower, that is an infallible cure for the epilepsy? Perhaps on the Monongahela, or the Potowmac, there may grow a root, that shall supply, by its tonic powers, the invigorating effects of the savage or military life in the cure of consumptions. Human misery of every kind is evidently on the decline. Happiness, like truth, is a unit. While the world, from the progress of intellectual, moral, and political truth, is becoming a more safe and agreeable abode for man, the votaries of medicine should not be idle. All the doors and windows of the temple of nature have been thrown open, by the convulsions of the late American revolution. This is the time, therefore, to press upon her altars. We have already drawn from them discoveries in morals, philosophy, and government; all of which have human happiness for their object. Let us preserve the unity of truth and happiness, by drawing from the same source, in the present critical moment, a knowledge of antidotes to those diseases which are supposed to be incurable.

I have now, gentlemen, only to thank you for the attention, with which you have honoured the course of lectures which has been delivered to you, and to assure you, that I shall be happy in rendering you all the services that lie in my power, in any way you are pleased to command me. Accept of my best wishes for your happiness, and may the blessings of hundreds and thousands, that were ready to perish, be your portion in life, your comfort in death, and your reward in the world to come.

An Account of an Hemorrhagic Disposition Existing in Certain Families*

JOHN C. OTTO, M.D.†
Philadelphia, Pennsylvania

ABOUT seventy or eighty years ago, a woman by the name of Smith, settled in the vicinity of Plymouth, New-Hampsire, and transmitted the following idiosyncrasy to her descendants. It is one, she observed, to which her family is unfortunately subject, and had been the source not only of great solicitude, but frequently the cause of death. If the least scratch is made on the skin of some of them, as mortal a hemorrhagy will eventually ensue as if the largest wound is inflicted. The divided parts, in some instances, have had the appearance of uniting, and have shown a kind of disposition to heal; and, in others, cicatrization has almost been perfect, when, generally about a week from the injury, an hemorrhagy takes place from the whole surface of the wound, and continues several days, and is then succeeded by effusion of serous fluid; the strength and spirits of the person become rapidly prostrate; the countenance assumes a pale and ghastly appearance; the pulse loses its force, and is increased in frequency; and death, from mere debility, then soon closes the scene. Dr. Rogers attended a lad, who had a slight cut on his foot, whose pulse "was full and frequent" in the commencement of the complaint, and whose blood "seemed to be in a high state of effervescence." So assured are the members of this family of the terrible consequences of the least wound, that they will not suffer themselves to be bled on any consideration, having lost a relation by not being able to stop the discharge occasioned by this operation.

Various remedies have been employed to restrain the hemorrhagies—the bark, astringents used topically and internally, strong styptics, opiates, and, in fact, all those means that experience has found serviceable, have been tried in vain. Physicians of acknowledged merit have been consulted, but have not been able to direct any thing of utility. Those families that are subject to certain complaints are occasionally relieved by medicines that are inefficacious when applied to others; and family receipts are often of greater advantage in restoring them, than all the drugs the materia medica offers for that purpose. A few years since the sulphate of soda was accidently found to be completely curative of the hemorrhages I have described. An ordinary purging dose, administered two or three days in succession, generally stops them; and, by a more frequent repetition, is certain of producing this effect. The cases in which the most powerful, and apparently the most appropriate remedies have been used in vain, and those in which this mode of treatment has been attended with success, are so numerous, that no doubt can exist of the efficacy of this prescription. The persons who are subject to this hemorrhagic idiosyncrasy, speak of it with the greatest confidence. Deceptions may take place from accidental coincidence; but when a complaint has often occurred, and been almost uniformly fatal without the administration of a certain medicine, and has constantly yielded when it has been given, scepticism should be silent with regard to its utility. Nor should our inability to account for the fact, upon the theory

*Reprinted from the Medical Repository, 6: 1, 1803. Printers P. and J. Swords, Faculty of the Physicians of Columbia College, New York City.

† Although references to what we now recognize as the disease hemophilia may be found in the Talmud and in the Medicinische Ephemeriden (1793), no clear account of most of the features of the disease was available until John Conrad Otto wrote his report in 1803. Otto introduced the term "bleeder" to designate these patients. His concise statement: "Males are only afflicted and all are not liable to it; though the females are free, they are capable of transmitting it to their children," embodies much of what is now known regarding the familial characteristics of the disease. Otto's report is largely responsible for the attention drawn to this group of patients by clinicians who followed him. (L.C.T.)

and principles we have adopted, be conceived a sufficient reason for disbelieving it. An attempt to explain the mode of operation of this valuable remedy might give birth to much speculation. As the affection has been attended with mortality, and there is generally a disposition to give relief as early as possible, experiments have not been made with the other neutral salts to learn their comparative effect; nor have medicines been tried whose operation might be supposed to be similar. The prescription being known to the whole family, application is rarely made to a physician, and when it is, it is rather with a view of directing him how to proceed, than of permitting him to make a series of trials and observations which might be at the hazard of the life of the patient. The utility of the sulphate of soda cannot arise from its debilitating effects, since it has been found serviceable when the previous depletion has been great, the strength much exhausted, and the system has evidenced symptoms of direct debility. Perhaps time will elucidate its mode of operation, and some general principles may be developed that may be applied to advantage in restraining ordinary hemorrhages; but reasoning upon what has been discovered to be useful in idiosyncracies, and applying it to the general constitution of human nature, must necessarily be vague and productive of occasional evil. In every case, however, a doubtful remedy is preferable to leaving the patient to his fate. The sulphate of soda has constantly succeeded when administered; but the prescription being in the possession of the Shepard family, the descendants of Smith, and the cases that have been attended by physicians not being very numerous, it is impossible to ascertain the various states of the system in which it has been given, or to form any correct conclusions respecting its manner of acting. No experiments have been made on the blood to discover if any or what changes take place in it.

It is a surprising circumstance that the males only are subject to this strange affection, and that all of them are not liable to it. Some persons, who are curious, suppose they can distinguish the bleeders (for this is the name given to them) even in infancy; but as yet the characteristic marks are not ascertained sufficiently definite. Although the females are exempt, they are still capable of transmitting it to their male children, as is evidenced by its introduction, and other instances, an account of which I have received from the Hon. Judge Livermore, who was polite enough to communicate to me any particulars upon this subject. This fact is confirmed by Drs. Rogers and Porter, gentlemen of character residing in the neighbourhood, to whom I am indebted for some information upon this curious disposition. When the cases shall become more numerous, it may perhaps be found that the female sex is not entirely exempt, but, as far as my knowledge extends, there has not been an instance of their being attacked.

The persons subject to this hemorrhagic disposition are remarkably healthy, and, when indisposed, they do not differ in their complaints, except in this particular, from their neighbours. No age is exempt, nor does any one appear to be particularly liable to it. The situation of their residence is not favourable to scorbutic affections or disease in general. They live, like the inhabitants of the country, upon solid and nutritious food, and when arrived to manhood, are athletic, of florid complexions, and extremely irascible.

Dr. Rush has informed me, he has been consulted twice in the course of his practice upon this disease. The first time, by a family in York, and the second, by one in Northampton county, in this state. He likewise favoured me with the following account, which he received some years since from Mr. Boardley, of a family in Maryland, afflicted with this idiosyncrasy.

"A. B. of the State of Maryland, has had six children, four of whom have died of a loss of blood from the most trifling scratches or bruises. A small pebble fell on the nail of a forefinger of the last of them, when at play, being a year or two old: in a short time, the blood issued from the end of that finger, until he bled to death. The physician could not stop the bleeding. Two of the brothers still living are going in the same way; they bleed greatly upon the slightest scratch, and the father looks every day for an accident that will destroy them. Their surviving sister shows not the least disposition to that threatening disorder, although scratched and wounded. The father gave me this account two days since, but I was not inquisitive enough for particulars."

On Irritable Heart*

A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences†

J. M. Da Costa, M.D.
Philadelphia, Pennsylvania

In this paper I propose to consider a form of cardiac malady common among soldiers, but the study of which is equally interesting to the civil practitioner, on account of its intimate bearing on some obscure or doubtful points of pathology. Much of what I am about to say I could duplicate from the experience of private practice; yet I prefer to let this inquiry remain as it was originally conducted on soldiers during our late war. The observations here collected were made on a series of upwards of three hundred cases. That so large a number were examined is thus explained. Shortly after the establishment of military hospitals in our large cities, I was appointed visiting physician to one in Philadelphia, and there I noticed cases of a peculiar form of functional disorder of the heart, to which I gave the name of irritable heart—a name by which the disorder soon became known both within and without the walls of the hospital. In a communication addressed to the Department in December, 1862, I further called attention to this form of cardiac malady, more particularly as it was observed subsequent to the Peninsular campaign. Afterwards, through the fostering care of the Medical Directors and Inspectors of this Military District, and the liberality and kindly interest of the Department at Washington, most of the cases of the kind were sent to my wards, thus enabling me to study the affection on a large scale. Some of the general facts recognized by this investigation I published in April, 1864, in the first edition of my *Medical Diagnosis;* but it was a mere outline, and the inquiry being pursued further, I intend here to give the complete results. The publication of the paper so long after the observations were made has been delayed by several causes; partly by want of leisure to analyze critically so large a number of cases; partly because it was my original intention to have offered this contribution as a report to the official history of the war; but chiefly because I found that, as I still from time to time encountered my former patients, I should by waiting have the opportunity of ascertaining the sequel to many of the cases recorded. And this—for reasons which will soon become evident—struck me in the examination of the subject as of particular value.

The class of cases which I am about to analyze was encountered in every army of the United States, and attracted the attention of many of its medical officers. Yet it cannot be said that ours was the first war in which it was noticed; for we find in the British Blue Book of the Crimean war, in the Report of the Hospitals of the Army in the East, as separate from morbus cordis, or carditis, pericarditis, etc., forty-five admissions for palpitation, and in another table, giving the return "invalided to England," sixty-two cases are thus classed; and I have seen here and there short statements which make it likely that the same affection was noticed in India, among Sir Henry Havelock's gallant troops. Nor can I believe that it has not always existed. Looking at the causes which produce it, it must have occurred among the troops in Sir John Moore's retreat, where, as Napier tells us, some brigades covered the retreat, fighting for twelve days, and traversed eighty miles of road

* Reprinted from *The American Journal of Medical Sciences*, edited by Isaac Hays, M.D. New Series, Vol. LXI, No. 121. Philadelphia, 1871. Henry C. Lea.

† Dr. Da Costa's masterful presentation dealing with the Irritable Heart was the first to consider the nature of this disorder in a comprehensive manner. In World War I the terminology was "The Soldier's Heart." In World War II a terminology which revealed a new understanding of the etiology was employed, namely, "Neurocirculatory Asthenia."

Space prevents the publication of Da Costa's paper in its entirety but pertinent excerpts indicating the splendid comprehension the author had of this important clinical disorder are herein reproduced. (G. G. D.)

in two marches; or among the devoted band by whose energetic movements Lord Clive conquered India; or among the victorious columns which, under Napoleon's guidance, passed by forced marches from the Rhine to the Danube, and compelled, at Ulm, the surrender of an army; or among the shattered and harassed forces which found their way back from the disastrous invasion of Russia. Yet, in examining, so far as I could obtain them, the documents bearing on these movements, I do not find the subject mentioned. But the disorder not being recognized, is no proof of its not having existed; for, when we reflect how almost entirely the accurate knowledge of diseases of the heart is the knowledge of our times, we can readily understand how difficult or impossible it may have been to have distinguished the less marked groups.

That the affection about to be described is not confined to troops engaged in actual warfare, may be judged by a statement of Coche,[1] that soldiers kept long under drill, are liable to functional derangement of the heart with palpitation; and, by various allusions and accounts, published of late years in Great Britain—prominent among which I may refer to an able lecture by Dr. Maclean, reported in the *British Medical Journal* of Feb. 1867,[2] in which the subject is incidentally mentioned—and in most of which the term irritable heart has been adopted. But, to this day, nowhere, whether as the result of the ordinary duties of the soldier or of actual war, has the subject, so far as I can find, been made one of careful clinical investigation. It is very possible that from inherent circumstances our war furnished more material of the kind than is likely soon to be met with again; for so many men called, by the tap of the drum, from civil pursuits, and sent without previous training into the field, is not a state of things likely often to happen. Whether among the Southern armies the same affection was common, I am unable to say; though from some facts that have been mentioned to me, I think it was. And it would be strange indeed, if men of the same race, transformed into soldiers under much the same circumstances, and, though operating oftener on interior lines, enduring on the other hand generally more privations, should have escaped.

[1] De l'Operation Medicale du Recrutement.
[2] See Medical News, May, 1867, p. 65.

So much by way of introduction. Let us now look at the medical aspects of the question.

General Clinical History. The general clinical history of many of the cases was this:—

A man who had been for some months or longer in active service, would be seized with diarrhœa, annoying, yet not severe enough to keep him out of the field; or, attacked with diarrhœa or fever, he rejoined, after a short stay in hospital, his command, and again underwent the exertions of a soldier's life. He soon noticed that he could not bear them as formerly; he got out of breath, could not keep up with his comrades, was annoyed with dizziness and palpitation, and with pain in the chest; his accoutrements oppressed him, and all this though he appeared well and healthy. Seeking advice from the surgeon of the regiment, it was decided that he was unfit for duty, and he was sent to a hospital, where his persistently quick acting heart confirmed his story, though he looked like a man in sound condition. Any digestive disturbances which might have existed gradually passed away, but the irritability of the heart remained, and only very slowly did the excited organ return to its natural condition. Or it failed to do so, notwithstanding the use of remedies which control the circulation; thus the case might go on for a long time, and the patient, after having been the round of hospitals, would be discharged, or, as unfit for active duty, placed in the Invalid Corps.

This may be stated to be a general summary of a considerable number of cases. But there were many others originating more suddenly, or without previous digestive disorder, presenting also marked disturbance or irregularity of the circulation, and having also the pain in the cardiac region well developed. I shall cite a few cases of irritable heart by way of illustrating these remarks:—

Case 261. *Irritable heart, previous marked diarrhœa; amelioration only of symptoms.*—William C., private, 140th N.Y. Vol., twenty-one years of age, single, and a farmer before he volunteered. He enlisted August 27th, 1862, had diarrhœa for about three months, and subsequently, while on a march from Harper's Ferry to Fredericksburg, had his attention drawn to his heart by attacks of palpitation, pain in the cardiac region, and difficulty in breathing at night. He remained, however, on duty, though not of very hard kind, until December 24th, 1862, when in consequence of a severe cold which resulted in

loss of voice, he was ordered from the front. Transferred from hospital to hospital, he was sent June, 1863, to the U. S. A. Hospital, at Turner's Lane, where I examined his case. This note expresses his condition at the time:—

"Height 5 feet 6 inches; weight 145 lbs.; measurement around chest, one inch below nipple, 35 inches; appearance that of fair health; gums rather spongy, says that they bled easily while in the field, and he thinks he had a slight attack of scurvy; appetite good; bowels regular; respiration 24 in the minute; pulse 122; impulse of heart extended, and very jerky; first sound decidedly deficient; second sound distinct; percussion dulness not increased; capillary circulation defective; hands bluish. On lying down, pulse becomes fuller, and is reduced to 98, and after a few minutes, to 90; on rising, after lying for some time, it only very gradually regains its previous velocity. He is still aphonic, probably from catarrhal laryngitis; was etherized before I saw him, but without effect on voice. He has had lately about two nocturnal discharges a week, which has been the case with him for years, excepting when in the field and suffering from diarrhœa, when he was free from them. Has occasionally spells of dizziness."

Case 87. *Irritable heart, chiefly from hard service; recovery.*—Wm. Henry H., private 68th Pennsylvania Vol., admitted into the Turner's Lane Hospital in Philadelphia, November 2d, 1863, having just returned from a furlough. He enlisted in August, 1862, at the time in good health, though he had suffered occasionally from rheumatism. He did a great deal of hard duty with his regiment. Some time before the battle of Fredericksburg, he had an attack of diarrhœa; after the battle, he was seized with lancinating pains in the cardiac region, so intense that he was obliged to throw himself down upon the ground, and with palpitation. These symptoms frequently returned while on the march, were attended with dimness of vision and giddiness, and obliged him often to fall out from his company and ride in the ambulance. Yet he remained with his regiment until July 4th, 1863, when he was wounded at the battle of Gettysburg. The wound healed in about one month; but the cardiac symptoms became worse, and violent palpitations ensued upon the slightest exertion, sometimes also whilst in bed, obliging him to rise. There was soreness in the cardiac region, and a constant dull pain. The impulse was extended, slightly jerky, 96, and of irregular rhythm, some beats following each other in rapid succession; the first sound was feeble, the second very distinct. The man did not look sick. Height 5 feet 7 inches; measured 31 inches around the chest one inch below the nipple; he did not smoke; chewed tobacco in moderation.

The patient did not improve under aconite; but under digitalis the impulse became quiet and 78, and on March 23rd, having previously done duty as orderly, he was detailed on police duty, and his treatment stopped. The heart continuing to act regularly, he returned to his regiment May 3, 1864.

These cases represent the cardiac malady most commonly encountered among soldiers. But side by side in the ward I soon noticed cases of hypertrophy of the heart, such as one meets with in civil practice; cases with all the forcible action of an increased organ, with its physical signs, its usual symptoms, often with a comparatively slow and laboured action; cases, therefore, wholly unlike the persistent excitement of the rapidly beating irritable organ. Holding at the time the common belief that functional and organic affections are widely separate, I failed at first to seize the fact that the apparently dissimilar states were in reality one, or rather, that one grew out of the other. But as patients multiplied I began to trace the connection; and observation showed me what I trust to demonstrate in this paper, the links connecting the disorders.

But to return to the purely irritable heart.

Symptoms.—Having indicated the general history of the malady, let us look in detail at the symptoms, taking for analysis merely the cases which were really of functional kind, or at least did not present decided organic change. And in the whole examination to follow, the remarks apply to this class of cases, unless the contrary is distinctly stated.

To investigate the palpitations first.

Palpitation.—Both the severity and frequency of the palpitations differed considerably in individual cases. In some the attacks lasted several hours, and were attended with increased pain in the cardiac region, and under the left shoulder. They were often accompanied by a great deal of distress, and were really painful. They occurred at all times of the day and night, varying in frequency from one to five or six attacks, or more, in the twenty-four hours. Yet there were cases that did not have them for days at a time. The seizures were, of course, most readily excited by

exertion, and might be then so violent, that the patient would fall to the ground insensible. This happened to some on the march or field of battle; or they fell in the ranks, and were taken prisoner. But attacks also occurred when the patient was quietly in bed, disturbing his rest, or waking him up; and some reported that they were worse at night, and early morning. They were very variously, sometimes whimsically, described. The rapid action was often commented on; but a "slow, hard" beat of the heart was also spoken of; and one soldier likened the cardiac derangement to the "fluttering of a chicken, when taken by the legs."

The fits of palpitation were not only associated with cardiac uneasiness and pain, but in some with headache, dimness of vision, and giddiness. As a rule, the patient could not lie on his left side, for fear of exciting them; but there were those who could lie as well, or better on the left side than on the right, or who could not lie on either the right side or back.

Cardiac Pain.—Pain was an almost constant symptom. I cannot recall a single well marked instance of the complaint in which it was wholly absent; and often it was the first sign of disorder noticed by the patient. It was generally described as occurring in paroxysms, and as sharp and lancinating; a few likened it to a burning sensation or spoke of it as tearing or as burning at times, and at others cutting; or as a "dull sullen" pain, becoming at times acute. In some cases no other pain happened than what occurred in these sharp attacks, or a mere feeling of uneasiness in the region of the heart existed; but in the large majority there was a substratum, as it were, of discomfort, or of dull heavy pain. In exceptional cases the pain was altogether of this character. Unwonted exercise or exertion would generally produce an attack of sharp pain, and a fit of palpitation was very apt to do the same; but the acute pain also happened without any unusual disturbance of cardiac action, and was, in truth, in rare instances, noticed to be decreased by exercise, or to be most severe when the patient was free from palpitation. Deep breathing was stated to make the pain severe, when it was otherwise but slight; cough produced a kindred result.

The chief seat of the pain was the lower part of the precordia, particularly near the apex. But it was not always limited to the region of the heart. It was spoken of as shooting to the left axilla, as passing down the left arm, which then felt numb; as being present under the left scapula; and as radiating from over the heart in all directions. The pain was associated with sensitiveness in the cardiac region, and this hyperesthesia was apt to be increased after attacks of palpitation. In cases which ended in recovery, both pain and tenderness gradually left.

The pain was not due to intercostal neuralgia. Thus, in Case 92 I find this description of the pain, "constant heavy feeling over outer and lower part of cardiac region, and slight soreness. Occasionally pain becomes sharp, and when sharp flies to back, at times to the head. There is also a slight pain, not, however, persistent, an inch or two above inferior angle of scapula. But there are no painful spots over the spine, or in the course of the intercostal nerves, and which might be attributed to intercostal neuralgia."

The latter affection undoubtedly, in some instances, existed, but it was as a complication. Just as pain in the back was occasionally encountered, due to excretion of abnormal ingredients with the urine, to muscular hyperesthesia, to sprains, and to the many causes which give rise to pain in the back in soldiers.

Pulse.—The pulse was mostly noted to be very rapid, varying from 100 to 140. In character it was small and easily compressible; it might or might not exhibit the abrupt or jerking character, which, as we shall presently see, is one of the chief peculiarities of the cardiac impulse, and this might have a certain amount of force which the pulse would lack. In some cases it was under 90, and was then apt to be fuller; these were, for the most part, the cases passing into cardiac hypertrophy. The pulse exhibits under any circumstances great variations; and especially in a case following an injury to the spine from a falling tree it changed about between 76 to 120, little influenced by any remedy employed. Slight irregularities in the succession of its beats, and, indeed, in the general rhythm, are very common. The pulse is always greatly and rapidly influenced by position. Thus, in one case in which, in the standing posture, it was from 105 to 108, it became shortly after lying down rather less than 80, and fuller, and then gradually rose to 98; in another case it is noted at 124 standing, at 94 lying; in yet another case in which it often reached 140 to 156, but in which, just prior to the observation, it was 128, it was reduced to 82 in the recumbent position; in yet another it was counted as 120 standing,

and as 84 when lying down. On the patient remaining for hours in the recumbent position, the pulse would in some cases slowly reach its minimum; in others it rose again by some beats after this posture had been for some time assumed; in all, the immediate effect of the exchange of position was most striking.

In the preceding remarks the pulse has been treated of when no palpitations existed at the time. These heightened it. But even when palpitation was not present, the beat at the wrist reached occasionally an extraordinary rapidity. Thus, on one case it was irregular, and seemed like a wave, slightly jerking and with intermissions; counted as accurately as possible, it was not under 192. Gradually, by rest and digitalis, it was reduced to 110.

I had several times the opportunity of studying the effect of acute maladies on the pulse, and I found that, instead of being rendered more rapid, it became slower. True, the recumbent position had something to do with the result, but the phenomena cannot be wholly thus explained. In one case, the patient for some days before he was attacked with typhoid fever, and when in his usual condition, presented a pulse of 124, which became 96 and fuller on lying down. After he had been for nearly a week in bed with typhoid fever, and had already commenced to take stimulus, it was still only 96; it then for three days was 104, 108 and 100, and very feeble; for the subsequent two days 96; for the next five days it gave a record of 84, 84, 84, 80, 86 and was very compressible, notwithstanding twelve to fourteen ounces of whiskey were daily taken, with considerable quantities of milk and beef-tea. For five days after this record it was still 80, and the heart sounds were sharp and valvular, as they had been before the fever. Convalescence was now beginning, but when the fever had entirely gone, and the patient had left his bed, the heart's action again became about 120, and once, during an attack of palpitation, rose to 200. In a case of typhus in a soldier with irritable heart, there was much delirium, and the pulse was noted as resistant, but as only 96; in Case 138 the heart beat 90 habitually, 80 while under the influence of digitaline, but became reduced to 48 during an attack of catarrhal influenza.

While treating of the pulse, I may allude to some other peculiarities of the circulation. The eye was sometimes noticed to be injected, and the lips of bluish colour. The hands were often bluish, and other portions of the skin mottled, and rendered pale on pressure; in truth, the whole capillary circulation was often palpably defective.

Respiration.—Shortness of breath, or rather oppression on exertion, was constantly complained of, and was a prominent symptom during attacks of palpitation. When the heart was acting in its usual way, a certain amount of embarrassment in breathing was also commonly spoken of, and was at times so severe that the patient was obliged to sit up in bed. Yet, notwithstanding all the signs of dyspnœa, it was astonishing that the respiration was so little hurried. And, as a general rule, it may be stated that this curious disorder presents the anomalous condition that increased action of the heart does not give rise to increased frequency of breathing; we find in it a peculiar pulse respiration ratio, and one just the reverse from that of pneumonia. To cite as proof a few cases of irritable heart: In Case 143, the pulse was 124, the respirations 25; in Case 300, I noted a pulse of 146, and respirations only 26 in the minute; and in Case 303, a pulse of 192, respirations 26. In Case 9 I found an exception, for the pulse was 84, the respirations 32.

Nervous Disorders.—These manifested themselves chiefly by headache, giddiness, disturbed sleep; and were symptoms which, though common, were not so constant as those already described. The headache was not apt to be persistent, but to occur in spells, and was generally of a dull, heavy character. It was more particularly noticed after severe attacks of palpitation; and might be associated with giddiness, and with increased heat and redness of face.

Dizziness was often complained of. It was increased by stooping; by exercise; and sometimes preceded the attacks of palpitation. In one instance, the vertigo was so severe that the man fell from his horse.

Jerking during sleep and disturbed rest were annoying symptoms. The unpleasant character of the dreams was frequently referred to; one soldier spoke often of dreaming that he was falling off high buildings.

The symptoms just referred to are all indicative of disturbed circulation in the cerebro-spinal centres. But there was also evidence of disorder of the sympathetic nervous system, as shown in the itching of the skin and excessive perspiration from which many suffered. Inordi-

nate sweating of the hand was several times complained of.

Digestive Disorders.—These were very frequent. All kinds of indigestions, great abdominal distension, and diarrhœa were symptoms constantly encountered. But they were symptoms having reference rather to the causation of the cardiac trouble than due to this; and we shall examine their bearing further on.

Urine.—There was nothing in this secretion of special importance; at least not so far as investigated in the usual manner. In some instances considerable quantities of oxalate of lime were found; and in others, the urine presented those variations which are common in the digestive disorders with which the affection of the heart was combined.

Physical Signs.—In describing the physical signs I shall first bring those together which are the most usual.

The *impulse* is almost always extended, yet not correspondingly forcible; rather, it is quick, and abrupt or jerky. When the hand is applied to the præcordial region, it may note the quick impulse happening in a regular manner, or it takes cognizance of the irregularity of rhythm of the irritable organ. Further, it may at times perceive the two sounds of the heart; feel them as it were. On listening to the heart, the first sound is found to be lacking in volume, feeble or short and valvular, and just like the second sound; and the valvular character of the first sound may be best appreciated a little to the left of the impulse. As recovery ensues, the first sound gradually regains its usual character, and it may do this, although when it originally came under observation it was almost extinct. The second sound of the heart is generally increased, and always very distinct; I met with but one instance in which it was the reverse. The sounds of the heart are freely transmitted beyond the cardiac region; the second sound may be heard very clearly defined over the carotid.

Sometimes the sounds of the heart are split. Thus in Case 219 the impulse was very irregular; there were double beats and intermissions, and one of the cardiac sounds—the irregularity made it difficult to determine which, though I think it was the first—was curiously broken, and sounded like the sudden motion of an oily slightly elastic or cartilaginous substance. Not even with a double stethoscope could a murmur be detected. In other instances the intermission every few beats now, or only every eighth or twelfth beat at another period, gave to the sounds following the perverted action at different times a different character.

But even where the rhythm is regular we meet with other modifications of the sounds. Thus, the first sound may be dull and not deficient, and this although, as in all the preceding cases, there is no increase in the cardiac diameters to denote enlargement of the organ. Nay, the sound may be dull and heavy, the impulse rather forcible, and yet percussion of the heart not indicate hypertrophy. Still these cases end, I believe, oftener in this way than those in which the more typical signs of the irritable heart are present.

Murmurs obscuring or replacing the cardiac sounds are not as a rule present; yet they are met with, and particularly is that form of murmur, systolic, chiefly above the apex, and not connected with venous hum or other signs of anaemia, which I have described as significant of functional valvular disorder. It has all the peculiarities there dwelt upon; in truth, it was a study of the cases now under analysis that first familiarized me with it; and until I found out its meaning I was often much puzzled to know whether I was dealing with a case of organic valvular trouble or not. The inconstancy of the blowing sound is of much value; in cases of perverted rhythm it may only be heard with the first beat succeeding the intermission.

Course of the Disorder.—Having discussed the symptoms and physical signs, it will be useful to inquire into the course of the malady. This mostly either gradually subsides, or it passes by degrees into cardiac enlargement.

When the disorder yields, the heart becomes less and less irritable, exercise no longer affects it so much the cardiac pain and soreness disappear, and finally the patient is again able to bear fatigue and undergo exertion; or in other instances, he is well as long as he is not too active, but his heart is always liable to be more disturbed by undue exertion or by excitement than the heart of a healthy person is. I shall give some illustrative cases, selecting partly those that returned to their regiments, but chiefly those that I had opportunities of observing after they left the service.

Case 34. *Irritable heart; recovery; return to regiment.*—Here the cardiac symptoms were very marked in June, 1862, the pulse 96 and feeble, the impulse jerky. He gradually recovered, the impulse lost its jerking character, the first sound

of the heart gained in volume, the rhythm of the heart became quite regular, its action much slower, and by August 5th, he could take exercise with impunity. After a furlough he was fully able to return to his regiment.

CASE 47. *Irritable heart; return to regiment.*—This case, when seen in July, had an impulse jerky and extended, a pulse of 100 and irregular; a feeble, indistinct, first sound. By September his pulse when quiet was 66, and became only 96 to 100 after running on the double quick; a slight hesitation was still observable with some of the cardiac beats. He was subsequently absent on furlough, and did guard duty; and before being sent to his regiment in December, bore active exercise well; the heart beat about 68 times in the minute, and was regular.

DIAGNOSIS.—The diagnosis of the affection has become evident from the preceding remarks, and I shall confine myself here to a few general statements, chiefly about matters that have not been explained or touched upon. And first, of the cases last discussed, and which were viewed as cases in a state of transition to hypertrophy. It is necessary to mention that in exceptional instances they are simulated by irritable hearts, in which the first sound is heavy, and the impulse rather forcible; but the percussion dulness is not increased, and whether we view them as cases arrested at the very beginning of organic change or not, it is certain that the heart returns apparently to a perfectly natural condition. In some instances of the kind it may be necessary to watch the effect of treatment—which, generally, rather rapidly influences the disordered organ—before a positive conclusion can be reached.

As regards the examples of hypertrophy we must bear in mind that fixing the boundaries of the heart only once is not sufficient for diagnosis, for increased dulness on percussion may be temporarily caused by engorgement of the cavities with blood. Again, both with reference to cases of hypertrophy and of irritable heart, we must remember, as above explained, that blowing sounds from excitement and functional valvular disorder are very common; and must guard against confounding the cases, on account of these murmurs, with valvular disease of the heart. I may add that I have known many a man discharged the service for organic valvular disease, who presented merely the combination of phenomena here referred to. The similarity may be greatly heightened by the coexistence of dropsy, a sign I very seldom noticed in the cases of hypertrophy, still more seldom in those of irritable heart; but which does happen in either, and when coexisting with a cardiac murmur may perplex the most skilful diagnostician. In Case 187 this combination was present, but all the signs disappeared and the man recovered. The dropsy of the irritable heart is limited to the lower extremity, and is apt to be very transitory.

Dilatation of the heart I encountered only very rarely. Where it existed it might have been confounded with irritable heart; but the extent of the percussion dulness, and the marked tendency to dropsical effusions were very significant features. Anaemic hearts are distinguished from irritable hearts by the history, by the murmurs at the base, the venous hum, the aspect of the patient, and the absence of cardiac pain. Occasionally the two affections are combined, but I have left out these instances in the analyses on which this paper is based.

It would seem scarcely necessary to speak of the differential diagnosis between irritable heart and phthisis. Yet they may be mistaken. Slight irritative coughs or attacks of bronchitis are not uncommon, perhaps more common than in persons whose circulation is not disordered, and with the disposition to shortness of breath and the rapid pulse may well mislead. Moreover, soldiers with irritable heart as well as with hypertrophy, may spit blood after fatigue or violent exertion, and thus the resemblance is strengthened. But the aspect of the patient, the pain in the praecordial region, the attacks of palpitation, and the absence of the physical signs of tubercle furnish the distinctive traits.

Lastly, it is impossible to discuss any malady to which soldiers are liable without discussing its being feigned. And a malingerer, as is well known, may keep up a rapid action of the heart by a tight bandage around the upper part of the abdomen and lower part of the chest. But, excepting if this be done, the imitation is a very clumsy one. The impostor knows nothing of the character of the cardiac pain. Further, making him lie down after undressing causes the heart to return to its natural beat; and then on his resuming the erect position, or walking around quietly, it will not, as an irritable heart does, regain its former frequency or irregular rhythm. And the peculiar physical signs of the irritable organ, and its persistently rapid action when examined under any circumstances save when the patient is in the recumbent posture, are traits which cannot be copied.

CAUSES.—In discussing the causes we are led to examine some of the most interesting questions connected with this inquiry. But in no part of it is it more difficult to arrive at fixed conclusions, for many causes seem at times to have combined, and it is scarcely possible, even by the most rigorous analysis, to fix specially upon one. In the subjoined table great care has been exercised to arrive at the probable causing element. The cases which have served as its basis have been only so far selected that doubtful or ill-marked ones have been excluded, and that those patients who were chosen, were for the most in good general health.

Analysis of 200 Cases

Fevers	34	17 per cent.
Diarrhoea	61	30.5 per cent.
Hard field service, particularly excessive marching	69	38.5 per cent.
Wounds, injuries, rheumatism, scurvy, ordinary duties of soldier life, and doubtful causes	36	18 per cent.
	200	100

This table requires some words of explanation. As regards the *fevers*, 29, or 14.5 per cent., were typhoid fever, or the so-called typhomalarial disorder, or pure remittent fever; only, however, very few of the latter: the other 5, or 2.5 per cent., were measles. And among the fever cases some noticed palpitation and shortness of breath on exertion during convalescence; but in the majority the cardiac symptoms did not become marked, certainly did not attract attention, until after return to duty.

Sixty-one cases of *diarrhoea*, or 30.5 per cent., represent certainly more than a mere coincidence. Yet even this number might be increased to about 35 per cent. if we take into account other gastro-intestinal affections which have been included in another category, such as obstinate constipation with occasional jaundice, or greatly swollen tympanitic abdomen. In a few of the cases only in which diarrhoea was thought to be the exciting cause, did the looseness of the bowels persist, or was it at least still readily excited by indiscretions in diet; in most it had ceased for a considerable time before the patient came under observation.

Hard field service was the chief assignable cause in 38.5 per cent. of the cases. Some of these had also had gastric or intestinal disorder, though not of persistent or active type. But constant and heavy duty on the picket line, or during active movements in the face of an enemy would develop the cardiac symptoms; or slight before, these increased and became marked after forced marches; or during arduous and exciting fighting and marching. In some instances the history was given of heavy marching having caused the cardiac disorder, but of diarrhoea having greatly aggravated it.

We come now to the last category in which 36 out the 200 cases, stand and here we meet with wounds, injuries, rheumatism, scurvy, and various other causes. I could find but extremely few instances in which a *wound* had even seemed to be the starting point, though in some the disorder was aggravated by it, particularly if on return to duty they saw at once much active service. *Strains and blows*, and similar injuries, had a much more direct influence. Case 240 was knocked insensible by a falling tree; Case 241 was prostrated by a sand-bag striking him over the heart; Case 249 was, in a hand-to-hand encounter, hit on the left breast with the butt of a musket; Case 287 strained his back while carrying railroad iron at the battle of Weldon Railroad.

Rheumatism was the undoubted cause in some instances. The rheumatic affection unquestionably also attacked the muscles of the heart, and under continued exertion, or on going back to duty soon after the seizure, the cardiac malady was manifest. In one case there had been rheumatic attacks before enlisting, and a slight cardiac derangement, which became a very annoying one on the man's going into active service.

With reference to *scurvy*, I found a condition of things very different from what might be anticipated. To say that it existed, or that there had been symptoms making it highly probable that it had existed, in five per cent., is to accord the fullest possible allowance. Judged by its usual symptoms, of spongy gums, of spots on the skin, of pseudo-rheumatic pains, it was a very rare causing element; and the long continuance of many of the cases, even after they had been home on furlough, had lived on the most varied diet, and while looking robust and well, does not make it seem as if a scorbutic state of system had had much to do with producing them.

In bringing this inquiry to an end, I may be permitted to point out what I believe to be its chief interest and value. To the medical officer it may be of service as investigating a form of cardiac disorder which every severe or protracted campaign is sure to develop. And from a military

point of view, further, it enforces the lessons, how important it is not to send back soldiers just convalescent from fevers or other acute maladies, too soon to active work; it suggests that their equipments be such as will not unnecessarily constrict, and thus retard or prevent recovery; that recruits, especially very young ones, be as far as practicable exercised and trained in marches and accustomed to fatigue before they are called upon to undergo the wear and tear of actual warfare; and it exhibits some of the dangers incident to the rapid and incessant manoeuvring of troops. True, on a movement executed on the double-quick may depend the issue of a battle, a forced march may determine the fate of a nation; and the time can never come when purely physical considerations can forbid, either one or the other, or dictate how often they may be ordered. But every commander should be made aware that in so using his men he is rendering some unfit for further duty, impairing others, and thus be led to count the cost of the frequent use of such active movements as carefully as he would the holding of a particular part of a line or the assault on another.

But the chief value of this inquiry is after all to the practitioner of medicine. It traces, I venture to hope that I may say establishes, the connection between functional derangement and organic change and examines the intermediate steps. And it is a contribution, based on trials made on a very extensive scale, towards the accurate knowledge of the action of remedies on the heart; showing, among the points, how a remedy may specially influence one of the elements of disorder without affecting the others.

Two Recent Reprints

Rapid Absorption of Substances Injected into the Bone Marrow*

L. M. TOCANTINS, M.D.†
Philadelphia, Pennsylvania

SUBSTANCES injected into the marrow cavity of the tibia of the rabbit and of the sternum of man appear to find their way immediately into the general circulation. That material so administered is taken up and utilized as rapidly as if it had been injected intravenously has been demonstrated in the following ways:

1. Blood replacement by intramedullary injection. A rabbit was bled of 20% of its calculated blood volume, by puncturing the heart and aspirating the blood slowly into a solution of sodium citrate. Twenty-four hours afterwards a needle with bevelled stylet was placed into the marrow cavity of the upper portion of the tibia, and blood, freshly removed from another animal, was introduced in an amount equivalent to that withdrawn the preceding day. The injection was allowed to proceed at the rate of about 5–7 cc per minute. Slight twitching of the leg after the injection started was the only disturbance observed in the animal. Seven animals were treated as described; 2 other animals were bled and allowed to recover spontaneously. Of the 7 treated animals 4 recovered their original (previous to the bleeding) erythrocyte and hemoglobin level within 24 hours after the intramedullary injection, 2 within 48 hours, and one died as a result of a hemopericardium. The last mentioned animal was the only fatality among all the animals that received various substances by the intramedullary route. None of the other animals showed any sign of distress during or after the experiments. In Fig. 1 is illustrated the response of the erythrocytes, hemoglobin and reticulocytes of a treated and an untreated animal.

2. Injections of glucose in experimental hypoglycemia. Four rabbits were rendered hypoglycemic by intravenous injections of a dose of insulin equivalent to 12 units per kilogram of body weight. Immediately after the appearance of a convulsion (usually within 3 hours after the injection) a 25 or 30% solution of dextrose (2–3 g per kilo body weight) was injected into the marrow cavity of the upper portion of the tibia at the average rate of 8 cc per minute. The abdominal reflex which was always absent during the convulsive period returned immediately after the end of the injection and there were no further convulsions. All dextrose treated animals recovered from the hypoglycemic reaction. An additional animal to which the dextrose injection was not given died 37 minutes after the first convulsion.

Rabbit B-85. Weight 3.3 Kg. Fasting 24 hours.

7-25-40 11:00 A.M.: Blood sugar (Benedict's method): 102 mg per 100 ml. of blood.
11:02 A.M.: 22 units of crystalline zinc insulin intravenously.
12:33 P.M.: 18 units of zinc insulin intravenously.
12:42 P.M.: 2 convulsive seizures; abdominal and corneal reflexes absent. Blood sugar: 64 mg.
12:50-12:52 P.M.: 20 cc of 25% glucose injected into the marrow of the tibia. Abdominal and corneal reflexes present at the end of the injection. No further convulsions.
12:54 P.M.: Blood sugar: 540 mg.
1:03 P.M.: Blood sugar: 363 mg. Animal alert and active.
3:50 P.M.: Blood sugar: 78 mg. Animal fed and watered.
7-26-40 9:00 A.M. Animal well. Blood sugar (not fasting): 152 mg.

3. Rapidity of spread of dye injected in the tibial marrow. A marrow puncture needle was inserted into the upper portion of the tibia of a rabbit. A plain 20 gauge needle was introduced into the heart and 1.5 cc of blood aspirated into 0.5 cc of 1.3% sodium oxalate. The needle was left in the heart and meanwhile 1.5 cc of a 1%

* From the Division of Hematology, Jefferson Medical College and Hospital, Philadelphia, Pa.
† Reprinted, with permission, from Proceedings of the Society for Experimental Biology and Medicine, 45: 292–296, 1940.

solution of Congo Red was injected through the tibial needle into the marrow cavity. At 10, 20 and 60 second periods following the end of the injection (duration of injection 7″) blood was removed from the heart through the indwelling needle. The specimens were then centrifuged and the color of the plasmas noted. The plasma was colored in the very first specimen, indicating that it took ten seconds or less for the material to reach the heart from the tibia. Similar results were obtained with a solution of fluorescein.

path of least resistance appears to be toward the venous system. In man the marrow tissue itself of the sternum, adjacent to the point of injection, was infiltrated to a limited extent, the mercury escaping chiefly into the outgoing venous channels; in the rabbit the rest of the tibia was entirely free of the injected material.

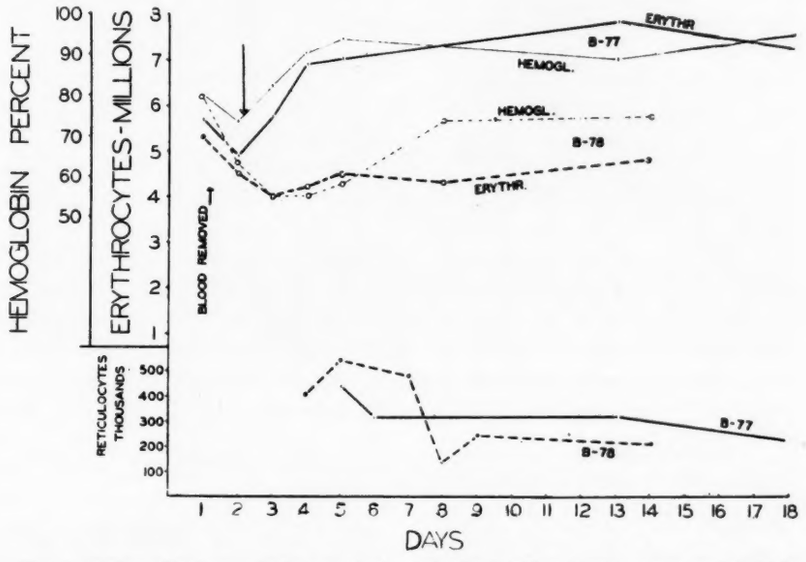


FIG. 1. Effect of intramedullary injection of citrated blood. Blood was removed by heart puncture from both animals (short arrow). Twenty-four hours later an amount of freshly collected blood equivalent to that removed was injected (long arrow) into the tibial marrow of Rabbit B-77.

4. Injection of mercury into the marrow cavity of the tibia of the rabbit and of the sternum of man. Fig. 2 represents an X-ray photograph of a human sternum and its collateral rib fragments removed at autopsy. A needle had been inserted at point A and about 1 cc of mercury injected under slight pressure. Almost immediately after the beginning of the injection, mercury was running out of the severed ends of the internal mammary veins on the under surface of the sternum. The same technic was followed in an attempt to determine the path of outlet of mercury injected into the upper portion of the tibia of a rabbit (Fig. 3). Mercury so injected apparently finds its way through veins in the bone cortex into the deep femoral. Just as in the human sternum, the

5. Gravity infusion of physiological salt solution into the sternum of man.* The sternal bodies of 3 adult men were punctured with a specially built gauge 15 needle, holding within it a gauge 18 needle with a bevelled stylet. Marrow was aspirated through the smaller gauge needle which was then removed. The lumen of the larger needle was then filled with physiological salt solution and connected with a salt solution infusion apparatus. In one man, complaining of bone pains, it was not possible to infuse any solution by this method; in the other 2, salt solution ran in by gravity readily, without discomfort, the infusion being maintained at rates varying between 5–10 cc per minute, for periods as long as 30 minutes when the experiment was discontinued.

Josefson[1] injected as much as 5 cc of liver

* From the wards of Medical Service B, Pennsylvania Hospital.

[1] JOSEFSON, A., *Acta Medica Scand.*, **81**: 550, 1934.

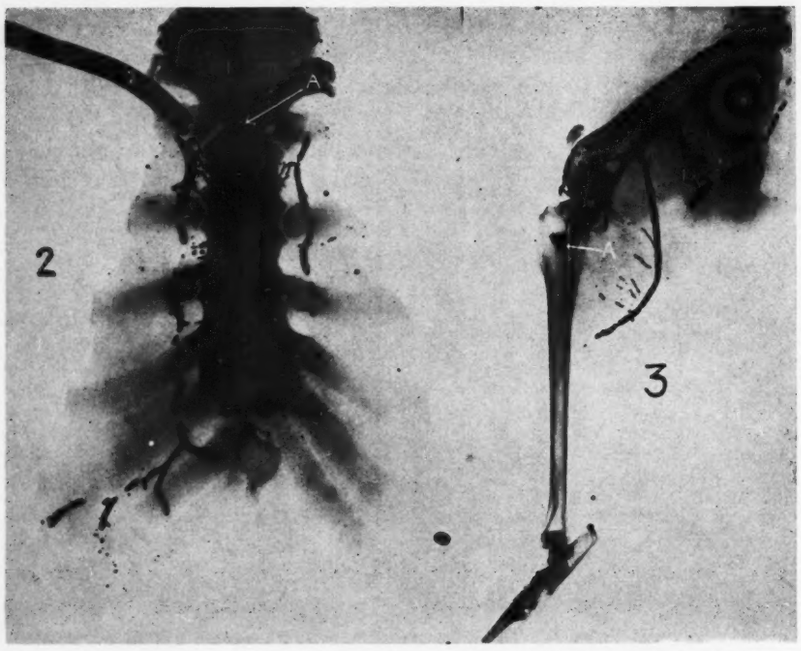


FIG. 2. Sternum and collateral rib fragments of an adult Negress. The thick line at the upper left corner is a hemostat clamping the cut end of the right internal mammary vein.
FIG. 3. Lower extremity of a rabbit. Amputation was carried out before injection. Arrows indicate points of injections of the mercury.

extract into the sternal marrow cavity of patients with pernicious anemia with the object of stimulating the bone marrow directly. A transient headache, sometimes severe, accompanied by vomiting, often followed these injections. These symptoms were probably caused by the massive rapid absorption of the drug, for they may be observed also after intravenous injections of liver extract. Radio opaque substances have been injected into the sternum of living patients with the object of studying structural changes in the marrow; the method succeeded only partially, because the injected material escaped into the general circulation before adequate photographs could be obtained.[2]

[2] BERTHET, G., BENDA, R., ORIENSTEIN, E. and DEPITRE, *Sang.*, **14**: 172, 1940.

The medulla of bones may, therefore, offer one more route for parenteral therapy when quick absorption is desired and prevailing circumstances (poor or obliterated veins, extensive burns or mutilations) make it difficult or impossible to use the common paths.

SUMMARY

Substances injected into the marrow cavity of the tibia of the rabbit and of the sternum of man are almost immediately absorbed into the general circulation. Blood and glucose solutions respectively, by intramedullary injection, corrected rapidly experimental anemia and hypoglycemia induced in rabbits.

Infusion of Blood and Other Fluids into the Circulation via the Bone Marrow*

L. M. TOCANTINS, M.D. *and* J. F. O'NEILL, M.D.†
Philadelphia, Pennsylvania

SUBSTANCES injected into the bone marrow enter the general circulation apparently unchanged and almost as rapidly as when injected intravenously.[1] In the parenteral administration of fluids to adult men it is sometimes impossible to use the intravenous route. Such is the case in widespread mutilations, burns, oedema, poorly developed, obliterated veins, states of shock. In the newborn and in early infancy the venous system is so poorly developed that the superior longitudinal sinus reached through the anterior fontanelle is often the only available direct path to the circulation. The risk of injecting substances through this route is high. These facts seemed to justify an attempt at a wide clinical application in man of the intramedullary route for parenteral therapy. Trial of this route has been carried out in 14 persons. Ten infusions of citrated blood were given by this method to 7 patients, plasma infusions to 2 patients and infusions of 5% glucose and salt solution to 4 patients. In 17 trials there was one failure (Case 10); little marrow could be aspirated from the sternum and no fluid could be injected by gravity. In 2 children the fluids were introduced into the tibia and femur. In all the other patients the sternum or the clavicle were used. From 100 to 1050 cc have been injected, the infusion needle being left in place for a duration of from 1½ to 16 hours. Some signs of discomfort are evident during the first steps of the procedure (aspiration of marrow and injection of salt solution with a syringe). Throughout the course of the infusion practically no discomfort has been felt. The average rate of infusion varied between 0.4 and 9 cc per minute. Strict asepsis has been observed throughout. Indications that the infused citrated blood had been rapidly absorbed were a substantial increase in the amount of hemoglobin and number of erythrocytes in the blood of the patients 24 hours after the infusion. Readings of the intramedullary pressure as obtained with a water manometer before the start and after completion of the infusion have not differed by a significant margin. The readings varied between 50 and 120 mm of water and often corresponded closely with readings of the pressure in the veins of the forearm. There have been no local or constitutional reactions as evidenced by clinical or X-ray findings following any of the infusions. The 2 children that received the blood infusions were under one year of age and in neither of them were there veins available for transfusions. The method and apparatus used and the results obtained will be described in detail elsewhere.

Within the limitations outlined the intramedullary route for the parenteral administration of blood and other fluids seems to have its indications and has proved to be feasible. Application of the method should be limited to such times as when the intravenous route is not available and only by those familiar with the technic and favorable points of approach. Work now in progress indicates that other bones may have equal or greater advantages over those previously employed.

[1] TOCANTINS, L. M. *Proc. Soc. Exper. Biol. & Med.*, **45**: 292, 1940.

SUMMARY

The intramedullary route for parenteral therapy has proved practicable in 16 out of 17 trials in 14 patients. Citrated blood, plasma, glucose and salt solutions have been infused without any immediate or delayed local or constitutional reactions.

* From Division of Hematology and Surgical Service B, the Jefferson Medical College and Hospital, Philadelphia, Pa.
† Reprinted, with permission, from Proceedings of the Society for Experimental Biology and Medicine, 45: 782–783, 1940.

Lectures at Bicentennial Exercises

The Long Follow-up: A Compensation of the Aging Physician*

O. H. Perry Pepper, M.D.
Philadelphia, Pennsylvania

As the title indicates, this article is to be devoted to a discussion of the opportunity for physicians to follow up interesting patients over a period of many years. Most follow-up reports give percentage statistics on the state of health and survival of a group of patients similar in diagnosis and therapy. Such reports seldom concern a time period exceeding perhaps ten or twenty years. It is my thesis that something can be learned from much longer observation of even individual patients. Certainly such a long-continued follow-up of a patient is interesting to the physician and offers him one of the very few compensations of his advancing years. I have chosen four examples not because the follow-up has been remarkably long but because each has been of peculiar interest to me. The topics are totally unrelated; one concerns the function of the spleen, the second a familial anomaly, the next the results of replacement therapy and the last a phenomenon of aging. Every elderly physician has favorite long-followed cases. No two would choose the same for a clinic such as this.

My first long time follow-up in this clinic is historical and concerns not an ailing person but a very healthy institution 200 years old. No one can boast of having watched this hospital from its birth through its adolescence up to its present robust maturity. None of us will live long enough ever to see the earliest sign of its senescence, if such should ever appear. We all pray and believe that no such involutionary change shall ever develop even in the distant future.

The Pennsylvania Hospital has had an amazing history. All of us would like to have served here during the days of the yellow fever epidemics or during the epoch when the wards were overflowing with cases of typhoid fever. We would like to have served with all the eminent men who have been on the staff. We are proud of any connection we may have had with this institution.

The first patient I ever saw in a hospital was a patient with erythema nodosum shown me by one of your famous physicians, Dr. Alfred Stengel, when as a first year medical student I accompanied him on his rounds. Two years later I was allowed to work in the summer in the Ayer Clinical Laboratory with Warfield Longcope who was then preparing his authoritative monograph on Hodgkins' Disease. In connection with this I published in the *Bulletin of the Ayer Clinical Laboratory* my maiden medical effort.[1] This was a very brief and unimportant report and I was amazed to receive from Sir William Osler a kind note of praise and a review of my article clipped from the *Lancet*. The review was so much better than my article that I am sure Osler wrote it himself and asked the editor to publish it as a gesture of friendship for the son of his former friend and associate during his days in Philadelphia at the University of Pennsylvania. That was just the sort of thing that Osler did for many young men and which made him so beloved and so stimulating.

Case 1. Our first long time follow-up of an actual patient concerns a man who had his spleen removed in 1915.

J. L. was forty years of age in 1915 when he was admitted to the University Hospital. His presenting symptoms were weakness, dizziness, dyspnea and edema, all of which had been increasing for two years. He had a sallow pallor and an enlarged spleen but otherwise the physical examination was negative.

The patient's blood count revealed a hemo-

* Brief for a Clinic presented at the Two Hundredth Anniversary Celebration of the Pennsylvania Hospital, May 4, 1951.

globin of 20 to 26 per cent and a red cell count of from 1,100,000 to 1,700,000. The white cells were a little low; the platelets were 100,000 per cu. mm. Although the resistance of the erythrocytes to hypotonic salt solution was normal, there was a marked increase in the excretion of urobilinogen and urobilin. A diagnosis of pernicious anemia was advanced by some but there was certainly a marked hemolytic factor present and splenectomy was determined upon. In the light of the patient's history since splenectomy it seems that the case must have been one of hemolytic anemia, congenital or acquired, and certainly not pernicious anemia.

After transfusions the patient's spleen, weighing 340 gm., was removed. Convalescence was uneventful. The blood count slowly returned to normal. I was able to follow him up for twenty-eight years when he was lost sight of. His general health had been excellent except for mild diabetes and a little lumbago.

Such a long survival with good health after splenectomy is by no means unusual but it raises some interesting questions concerning the function of this mysterious organ. The concept of overfunction or dysfunction of the spleen is generally accepted today under the term 'hypersplenism' with its pancytopenia. However, we have no corresponding hyposplenism and total removal of the organ causes no recognized syndrome.

We can remove one of the lungs, kidneys, adrenals, gonads or parathyroids with impunity; we can totally remove the thyroid, the pancreas, both the parathyroids or both the adrenals if we then supply adequate replacement therapy. We dare not remove the brain, heart or liver. The spleen alone of the unpaired organs can be totally excised and health is unimpaired without replacement therapy. Has the spleen then no function? Is it a vestigial structure no more important than the appendix? Certainly there is no evidence that any other tissue assumes any new function when the spleen is removed nor that the splenectomized individual suffers any harm.

The functions which have been attributed to the spleen are many and include its action as a reservoir for blood to be called upon in an emergency. Perhaps our ancestors needed this more in those days of primitive existence. Also, various ideas concerning a possible function in the destruction of erythrocytes and platelets have been advanced but no satisfactory proof of these is at hand. Recent observations suggest hormonal control of some of the elements of the blood. However, there is one peculiar phenomenon which does follow total splenectomy and that is the appearance of Howell-Jolly bodies in some of the circulating erythrocytes. Sixty years ago Howell described these small granules and Jolly did so later. There is usually but one in a red cell; it stains as does nuclear material and these bodies are commonly thought to represent a residual particle of the red cell nucleus. However, they have been seen in nucleated red cells.

These Howell-Jolly bodies are occasionally seen in pernicious and other anemias and leukemia; always, however, in the presence of a definite anemia. In none of these conditions are these bodies as numerous as they become after splenectomy and only after splenectomy do they occur with a normal blood count. If there is an accessory spleen left in the patient, these bodies do not appear. Our patient showed no Howell-Jolly bodies before his spleen was removed; they appeared promptly after the operation[2] so we can feel sure that no accessory splenic tissue remained. Twenty-eight years after the splenectomy I had the opportunity to examine the patient's blood. The count was normal but the Howell-Jolly bodies were still present.

I have never heard of the patient's death; and although he would now be seventy-six years old, I had hoped to present him to you today. Sad to relate he has moved, but whether to another world or not I cannot find out. This is disappointing and limits my follow-up to twenty-eight years, but certainly long enough for our purpose.

This, I believe, is the longest persistence of this phenomenon reported in the literature. It would seem that it should give us some inkling of some function of the spleen but it does not actually shed any light on the mystery. Whatever the condition which in the first place called forth the Howell-Jolly bodies after the splenectomy, it was still in existence twenty-eight years later.

Case II. Our second follow-up surely deserves to be termed long, for it covers five generations of a family. It concerns a congenital anomaly.

The patient who aroused our interest was a white male fifty-one years of age. He was admitted to the University of Pennsylvania Hospital

in 1935 with a complaint of duodenal ulcer. During ward rounds I examined him and happened to pass my hand over his skull. To my amazement I felt two holes in the skull under the scalp. Each admitted a fingertip much as though one was palpating a bowling ball covered by a thick cloth. The holes were symmetrically placed on each side of the midline at the upper posterior aspect of the head.

Our group was interested and were vainly speculating on these openings in the skull when the patient stated that similar "holes" were present in other members of his family. He remembered as a child being rewarded for good behavior by being allowed to feel the "holes" in his grandmother's head. Naturally I was very interested and went to work with Dr. Eugene P. Pendergrass to learn the nature of the holes and their presence or absence in all the available members of the patient's family.

Roentgenograms of the patient's skull showed that the holes were each a large, rounded defect in the parietal bone in the exact position of the usual pin-sized parietal foramen. Our roentgenologic department had never seen this anomaly and there was no mention of it in roentgenologic literature. We thought we perhaps had found something new, but a search of other branches of literature revealed reports of it even as long ago as Lancisi in 1707. Hyrtl in 1865 and Piersol in 1902 reported anatomic specimens, and Pamperl in 1919 collected data on thirty-six skulls with such "holes." He named the condition "foramina parietalia permagna." Goldsmith in 1922 reported in *The Journal of Heredity* a family named Catlin with sixteen of fifty-six members presenting the anomaly. Unfortunately the title of his paper was "The Catlin Mark," so his report was lost sight of for years. In 1927 Greig published a complete review of the subject and added a description of two skulls from the museum in Edinburgh.

Of all these instances very few have been recognized in life and we were fortunate to be able to study this family. The grandmother was dead but the evidence of her having the anomaly was very satisfactory. The patient's mother, aged seventy-seven, was examined and had very large defects easily found by palpation. The patient and his son did, also. His sister had smaller but still abnormal foramina. Two of her children had foramina of top normal size, another had larger holes and the fourth was normal.

We reported on this family in 1936,[3] pointing out its importance in diagnosis as it would be easy to mistake the lesions for the results of Hand-Schüller-Christian disease, syphilis, secondary neoplasm, trephine openings and so forth. In fact, some of these skulls in museums had been labeled as the results of surgery. We emphasized that no harmful results seem to be caused by the anomaly.

Now, fifteen years later, we have started to examine the fourteen grandchildren of our original patient. These represent the fifth generation in this family. Recently we have examined eight of the fourteen children of the fifth generation. Of these only one shows an abnormal parietal foramen of small size and that on only one side. This baby is a grandson of the sister of our original patient. Our patient's son had large foramina but his three children show none, nor do the other grandchildren of his sister. We have so far been unable to examine the six others but already we have enough evidence to justify the statements that the anomaly has occurred in five generations and that it probably is not a dominant trait. It can occur in either male or female and can be transmitted by either sex. It would appear to be fading out in this family.

A follow-up of an anomaly in five generations and actually observed by us in four is about as long a follow-up as is possible during the life of one physician. This study gives a cheering view of the manner in which many anomalies cease to plague the coming generations.

As a result of our publication another family with the same anomaly was brought to our attention. In this Negro family there fortunately were two young children in whom we were able to follow the process of ossification of the skull. In both these infants the normal closure of the parietal foramina stopped and large "holes" were left in what otherwise are normal skulls.[4]

Case III. Our third long time follow-up does not at first glance seem to deserve mention but there are certain features which are interesting and almost unique. It opens up the question of patients with diseases formerly fatal but now kept in abeyance for long periods by replacement therapy.

In 1917 chicken pox of no unusual severity developed in a boy nine years of age. He had previously been healthy but was a bed wetter

and this increased after the chicken pox. His mother noticed that the sheets which he wet dried stiff, and his father, a physician, interpreted this correctly and found sugar in the urine.

At that time, in 1917, a diagnosis of diabetes mellitus in a child of nine was equivalent to a death sentence. We had no therapy to offer other than limitation of diet and careful efforts to avoid acidosis and coma. It was a tragic situation, hard for those to appreciate who did not see it at first hand. Continued semi-starvation was painful to enforce on a child. This boy, at the age of nine, weighed 84 pounds; five years later in spite of considerable growth in height he weighed 80 pounds, a loss of 4 pounds in five years.

That he survived at all for those years was due to the intelligent and unceasing care of his parents. Nevertheless, his condition steadily deteriorated. By 1923 he was a tall, very emaciated, pathetic youngster of fourteen. He had to keep to a very limited diet but constantly had glycosuria and ketonuria. In 1922 his condition was so bad that his parents and I discussed whether there was any justification for further efforts to save him. The alternative was a liberal diet, a short period of comfort and terminal coma. We decided to continue the struggle for "something might turn up."

It did! In March, 1923, our patient received his first dose of insulin and his first adequate meal in five years. He was among the first patients to be started on insulin therapy in this city. He did wonderfully well, again due to his physician father and conscientious mother. In fact he did so well that I lost sight of him for years only to have him turn up in class in the University Medical School. What a transformation from the near-skeleton of eight years before; now he was a husky, healthy man.

Today he is the head of a large laboratory; he is in perfect health and weighs 152 pounds but, of course, is still on insulin. He is taking 48 units of protamine insulin and 12 of regular insulin daily. He has had diabetes for thirty-three years and has been taking insulin for twenty-eight years. These periods are not rare. The important point in this case is the survival of a juvenile diabetic for five years without insulin and the "turning up of something" just in time to save his life. The latest item in this thirty-three-year follow-up is the arrival recently of a healthy son.

There are many morals in this dramatic story but they are obvious and need not be detailed. They are embodied in two sayings: "Don't give up the ship" and "Meticulous care helps every cure." To me this case has given perhaps the greatest satisfaction of any in my medical life, but the credit primarily belongs to his parents. It does not take many such experiences to make a physician glad he chose the medical profession.

Of course, replacement therapy will keep many patients with various diseases formerly fatal alive for long periods. We do not yet know all about the late stages of such cases and there are diagnostic pitfalls ahead when some other ailment develops in these individuals.

CASE IV. The fourth long time follow-up I wish to discuss concerns a geriatric problem. One would scarcely expect this since the geriatric patient obviously has no anticipation of survival for many years. But the problem is confused by the question of what puts a patient in the geriatric group. Is it simply a matter of years or does the presence of physical changes usually seen in the aged determine the matter? This gets us into still deeper water, for we meet the problem of whether certain changes should be classified as senescent or senile. It is easy to say that the phenomena of senescence are physiologic and those of senility are pathologic. But this does not help us much as the distinction between senescence and senility is far from clear.

In the list of so-called senescent changes one finds such varied items as gray hair, presbyopia, arcus senilis, loss of vibratory sense, osteoporosis and achlorhydria. These certainly must vary in their significance, and premature graying of the hair, such as occurs in some families, is admittedly no evidence of aging. On the other hand, the deposit of fat globules around the circumference of the cornea known as the arcus, or if it forms a complete circle, the circulus senilis, is usually accepted as evidence of senescent change. Occasionally, however, this is seen in healthy, young persons and it seems to run in families.

A friend of mine had a marked arcus senilis when in college fifty years ago. As a medical student I learned of the grave significance of this and in my omniscience I worried greatly over the early demise of this young man. Today at the age of sixty-nine he is in perfect health although the arcus has become a circulus. I have watched it increase for about fifty years

and have long since ceased being alarmed for him.

We know nothing of the reasons for the arcus senilis and, until we do, we had better not use it as a signal of senescence. It is interesting that Nascher, the author of the first good text on geriatrics, published in 1914, is said to have had an arcus senilis while in medical school. It is quite possible that his interest in diseases of old age was initiated by the discovery of his own arcus. He, too, lived to old age.

Actually, we need to know a great deal more about both senescence and senility. Every physician has seen a young man with markedly tortuous temporal arteries live in good health for many years without ever developing the anticipated arterial disease. In fact, the tendency today is to belittle the importance of arteriosclerosis in the production of the phenomena of aging. For example, evidence is available to suggest that the failing heart of the aged should not be called "arteriosclerotic heart disease" but, admitting our ignorance, some term such as senile heart or presbycardia should be employed.

None of the usually accepted phenomena of aging are sure evidence. We must take every opportunity to observe over the years individuals who develop any one of them at an early age. By doing this we may someday fit the contradictory facts into an understandable pattern. It is for this reason that I selected this last topic for mention in spite of its familiarity to everyone.

COMMENT

These four examples of the long follow-up are individually of some interest and, taken together, it seems to me that they illustrate the satisfaction and possible value of the following up of a patient over many years. The study of a case at a given moment may yield useful information, and so does the usual follow-up of a group of cases of some one disease. However, the long follow-up of even a single patient offers a method of gaining insight into the processes of disease from still another point of view. It may well be that this approach to the problem will give us data which can be obtained in no other way.

All that is necessary for a long follow-up is an adequate study of the patient in the first place, the keeping of careful records and an alertness for interesting problems. Also, of course, you must have a keen desire and curiosity to watch for yourself the life story of a patient and of his disease. If you will do this, you can rest assured that you will be repaid by the facts observed and in the gratification to be gained in some cases from the continued life and health of your patient. These several points of view seem to me to justify my title that the aging physician finds some compensation in the opportunity which age brings him, to watch his patients and their diseases over the years. I hope that the examples presented in this article are sufficient to prove this point.

I forgot to mention that in order to watch your patients over many years you must yourself live long. To do so one must maintain a vital interest. Something must make life worth while and what could be better than the continued observation of the interplay of man and his diseases.

REFERENCES

1. Pepper, O. H. P. Report of a case of Hodgkin's disease with general eosinophilia. *Bull. Ayer. Clin. Lab. Pennsylvania Hosp.*, No. 4: 22, 1907.
2. Pepper, O. H. P. and Austin, J. H. A twenty-eight year follow-up on a splenectomy for hemolytic anemia. Persistence of Howell-Jolly bodies. *J. A. M. A.*, 122: 870, 1943.
3. Pepper, O. H. P. and Pendergrass, E. P. Hereditary occurrence of enlarged parietal foramina. Their diagnostic importance. *Am. J. Roentgenol.*, 25: 1, 1936.
4. Pepper, O. H. P. and Pendergrass, E. P. Observations on the process of ossification in the formation of persistent enlarged parietal foramina. *Am. J. Roentgenol.*, 41: 343, 1939.

Recent Trends in Poliomyelitis Research*

JOHN R. PAUL, M.D.
New Haven, Connecticut

MAY I first take this opportunity to express my appreciation for having been included among the speakers, and this is mentioned for several reasons: first, to testify to my pride in being an alumnus of this Institution and of the Ayer Clinical Laboratory, and secondly, because of an incident which may concern us here. Twenty-five years ago, in 1926, Mr. Daniel D. Test, then superintendent of this hospital, commissioned me (as Director of the Ayer Clinical Laboratory) to go to Baltimore to invite the late Dr. William H. Welch of Johns Hopkins School of Medicine to come to Philadelphia to give the keynote address at the 175th Anniversary of this Hospital, which was to be celebrated that spring. I went to Baltimore as bidden but returned with my mission unfulfilled because, unfortunately, Dr. Welch could not accept the invitation of the Board of Managers. He seemed genuinely sorry and he did say, "If you let me off this time, I will promise faithfully to be present at the 200th Anniversary." And so I like to think that the spirit, at least, of Dr. Welch is here today attending this celebration of which he would eminently approve. From this same platform I have heard him eulogize the place which the Pennsylvania Hospital has held in the history of American medicine as perhaps no one else from outside of Philadelphia could ever do.

Before getting on with my subject there are a number of former members of the Pennsylvania Hospital staff whose names should be mentioned. These are Drs. Simon Flexner, Paul Lewis and George Draper. We shall pay tribute to their work in this brief review.

Before attempting to give a progress report on research work on poliomyelitis I must say that one has a right to inquire whether or not it is worth it. Has any real progress actually been made recently in man's struggle to *control* poliomyelitis? The prevention of this disease is, as far as I am concerned, problem number one. There have been great improvements in the aftercare of paralytic patients. New measures have been introduced for the relief of pain during the acute disease and for saving lives in the more serious cases, but in the field of prevention—no. This may be a sad commentary on the tremendous amount of effort, time and money which have gone into the attempts to solve this question. There has been much publicity about these efforts and we have been repeatedly told by the newspapers that a vaccine is just around the corner. Indeed, hopes ran high that this disease could be brought under control as long as forty years ago. You may well ask how medical scientists can explain their failure and what have they been doing all this time, for if there is one statement that can be made with confidence about poliomyelitis it is that practical achievements in its control cannot be listed among the medical successes of the past two decades. These decades have witnessed such great strides in the control of other infectious diseases that it may be hard to believe that nothing practical has been achieved in the prevention of poliomyelitis; that there are no specific drugs effective in treating poliomyelitis comparable to those which have been recently devised for bacterial diseases through the use of sulfonamides and antibiotics. But to say that research is being actively conducted in an effort to solve such problems in poliomyelitis grossly understates the magnitude of these efforts.

The most hopeful methods for *controlling* the spread of this disease should logically follow two lines: (1) the attempt to eliminate the virus from a community by so-called sanitary or quarantine measures and (2) the attempt to bolster human resistance by immunization, as one would with vaccination in a campaign against smallpox.

As to the first approach, there is agreement among students of this disease that poliomyelitis is generally spread by contact between persons;

* From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn. Read at the meeting to celebrate the Two Hundredth Anniversary of the founding of the Pennsylvania Hospital, Philadelphia, Pa., May 3, 1951.

however, it is more complex than that, for in most parts of the world the prevalence of poliomyelitis is influenced or even dominated in a mysterious manner by season or climate. No satisfactory reason has as yet been proposed to explain the fact why epidemics of poliomyelitis in this part of the world occur at so much higher a rate in the summer than they do in the winter. In seeking an explanation there are two possible approaches: Either something happens in the summer which enormously facilitates the spread and dissemination of the virus throughout a community or something happens which makes some people, the non-immune people, enormously more vulnerable and far more apt to acquire the disease than at other times of the year.

As to eliminating the virus from a community, the first obvious question here of course is whether there is an *extrahuman* reservoir of virus which operates better in summer than in winter; in other words whether the disease may not be spread by agents other than infected persons, for instance, by insects or contaminated food or water, which might be "eliminated." One cannot make dogmatic statements as to whether water, food or flies may on occasion be infectious. That poliomyelitis has been found under natural circumstances on food (contaminated by flies) and on flies during epidemics there is no doubt, but one cannot yet attach any special epidemiologic significance to these possible sites or objects. There is at least no evidence that flies are an essential link in the chain, as are mosquitoes in the transmission of malaria, when they carry a parasite, or in yellow fever, when they carry a virus. However, a good deal of the mystery about the spread of poliomyelitis vanishes with the recognition that unlike other contact diseases, such as measles in which the disease passes from one *recognized* case to another, the spread of poliomyelitis apparently occurs largely through *mild* cases, many of which are so mild that their recognition quickly reaches the vanishing point. The evidence is convincing that during an average epidemic of poliomyelitis those individuals who are ill enough to become paralyzed represent only a small fraction, perhaps only 1 per cent, of the total who are infected and infectious. If we include the non-paralytic and abortive cases of poliomyelitis we have a somewhat larger fraction, perhaps 2 per cent, leaving some 98 or 99 per cent or more of individuals who become infected without symptoms but who are capable of spreading the disease to others. Thus the ratio of the visible to the invisible cases may be of the order of 1:50 or 1:100 in a disease which spreads from person to person insidiously and which severely injures one person and immunizes some ninety-nine others. Our thoughts about its control should be conditioned by this concept.

We have, therefore, an enormous number of potentially infectious individuals at large in a community during an epidemic and there is no means of labeling them as such or controlling their activities. The hope for elimination of the virus from a community by the control of human activity through quarantine measures is thus not good. Besides, even if such an attempt were completely successful, it might lead to an undesirable result. It might leave us with no immunity at all—like Eskimos.

As a matter of fact some such elimination of virus from the community is going on automatically, for infants today are not exposed to as much virus as they were in our grandparents' time, in this country at least. In our grandparents' time poliomyelitis was a disease of infants—the true "infantile paralysis." Indeed, according to physicians in New York City at the turn of the century the malady was rarely seen in children over six years of age. Today we find not only in the northern half of this continent but also more particularly in Scandinavia and in Europe and Australia that poliomyelitis is not a disease limited to infants but is often seen in children of school and teen age. Perhaps 25 per cent of patients in New England today are fifteen years of age or over. This change in the age level of incidence has not taken place everywhere, for the disease is still concentrated among infants in certain primitive and tropical countries. Hence one might suppose that the alteration in the incidence of the disease is somehow associated with our twentieth century way of life, such as the changing character and composition of our population or the curtailment in the size of families, or even our sanitation. Perhaps highly modern "hygienic methods" may have reached the point at which infants and young children are being protected from exposure to this virus today more than was the case in our grandparents' time, but our modern "hygiene" has not reached the point which protects them later in life (that is during childhood or adolescence); so the occasional clinical attack of poliomyelitis has been postponed—not

eliminated. It is questionable, of course, whether this is good or bad.

I will reiterate that when it comes to preventing poliomyelitis the idea of eliminating the virus from a given community in order to produce a local "virus-free" environment does not seem to be the best one and other methods appear to be more hopeful.

The second approach is that of immunization. What is obviously needed in the struggle to prevent poliomyelitis is some means of bolstering the immunity of children (and adults) to enable them to resist the infection induced by periodic exposure to the virus; that is, one might combat poliomyelitis as we now combat smallpox, diphtheria and whooping cough, by vaccination. Since no vaccination for poliomyelitis is available, our predictions can go no further. However, there are two lines of approach which might be taken: (1) the use of inactivated virus, so-called killed virus, which would yield a vaccine comparable perhaps to the bacterial vaccine used to control typhoid fever; (2) a live vaccine in which one would hope to use a modified virus comparable perhaps to that used to protect against smallpox by the use of vaccinia inoculations or that used in vaccination against yellow fever. This is the quest in which many laboratories are involved. It would seem unlikely, however, that an effective vaccine will be reached by investigators working on mice and monkeys alone, for the real experiment will come when the new vaccines are tried on man.

Another type of approach in this direction is the use of immune sera as a means of inducing *passive* immunity in order to tide individuals over an epidemic period. For this procedure large numbers of individuals within a given epidemic area would have to be given this immune sera, presumably in the form of gamma globulin and perhaps several times during the epidemic. Indeed, it is not too much to hope that during the transient period of protection artificially produced in this way the protected individual could be happily exposed and conceivably develop the so-called "passive-active immunity" in which Dr. Joseph Stokes, Jr., of this city has been interested. This would be a useful plan but one difficult to control. It is still in the experimental stage.

As regards work with the virus itself, you will recall that it is a fastidious virus as regards host range and altogether difficult to work with. It is extremely small as viruses go, and one which has not yet been clearly visualized in the electron microscope. It is very labile in some respects and yet in others is quite resistant against chemicals. Furthermore, before we can hope to have a vaccine there must be a broader knowledge of the virus types, for within the poliomyelitis family there are three or perhaps four immunologic types which include the so-called Lansing, Brunhilde and Leon types. The question arises, of course, as to whether, if a vaccine is to be produced, the average child should be immunized to all three types before he or she can be properly considered to be immune to poliomyelitis, because it has been shown repeatedly in the laboratory (particularly in work on feeding chimpanzees) that whereas type-specific immunity exists, an animal can be reinfected with a heterologous strain. This by the way is the reason usually given to explain the fact that the same individual may contract poliomyelitis more than once, namely, it is an example of becoming infected by multiple strains. It would seem, therefore, as if a multiple strain or so-called polyvalent vaccine would have to be used. Furthermore, it is still unknown whether or not there are only three strains; there may be several more as yet undiscovered.

These are some of the reasons which have delayed the progress on work in actively immunizing people against poliomyelitis.

Speaking of multiple strains, one should point out that running closely parallel to virus research in poliomyelitis has been the finding in 1948 by Dr. Dalldorf at the New York State Department of Health at Albany of a whole new family of viruses: the Coxsackie viruses. He discovered a new and inexpensive laboratory animal, the suckling mouse, and thereby opened up a veritable Pandora's box of new agents. It was an example of uncovering the etiologic agents before one discovered the diseases which they cause, many of which are characterized clinically by symptoms suggesting acute myositis and meningeal reactions although one particular member of this great family of diseases was known prior to 1948. This was epidemic pleurodynia. None of these Coxsackie viruses, to my knowledge, cause paralysis and none, unfortunately, are known to give rise to immunity against poliomyelitis.

But to return to poliomyelitis virus, much that I have said so far has been pessimistic. On the brighter side of the picture one can point to the work of Dr. Enders and his colleagues at

the Children's Hospital in Boston in which he has succeeded in cultivating the virus in non-nervous tissue culture. Unfortunately, the titer of virus grown in this manner is not high; it has not yet been shown to be transferable to eggs but there is no doubt that much progress will be made along this line, and perhaps thereby the virus can be attenuated.

Regarding diagnostic tests, there is also hope there. This rests on the recent announcement of a *complement-fixation test* which Drs. Casals and Olitsky of the Rockefeller Institute have described. By an ingenious method of adapting the virus to very young mice they have succeeded in surmounting what was always the greatest obstacle to finding an antigen rich enough in virus to be useful in detecting antibodies by the complement-fixation technic. There has been little practical, clinical use of this test as yet but of the dozens of others that have been proposed within the last generation this one promises far and away to be the best.

Finally, I would like to mention observations which relate the element of trauma, surgery and even injections for immunization to causative or so-called precipitating factors in poliomyelitis. For more than seventy-five years the observation has been recorded in medical literature that injury, exertion or strain experienced by a given patient in the early stages of or immediately prior to the development of acute poliomyelitis seems to exert an unfavorable action on the clinical course of the disease, often resulting in more severe and extensive paralysis than would occur in the average case. Studies by Dr. Russell of Oxford University in England and by Dr. Horstmann in the Yale Poliomyelitis Study Unit at New Haven indicate that if severe trauma, exertion and stress are experienced on the day or two immediately preceding the onset of paralysis, the prognosis is less favorable than if this had not happened.

There is also an accumulating mass of evidence to indicate that operations about the mouth, for example, tonsillectomy or tooth extraction, if performed within three months of the onset of the disease exert unfavorable effects, not only increasing the likelihood of acquiring the paralytic form of the disease but also in acquiring the severe bulbar form. Evidence is also accumulating that as small a bit of trauma as diphtheria immunization or pertussis immunization, if given within a period of a few weeks prior to the onset of poliomyelitis, may give rise to paralysis of the limb which was injected. These indications have come to us from England and Australia in a number of reports published early last year, and surveys from last summer are now beginning to come in from this country to show that in a small percentage of cases this element of trauma, i.e., pre-illness immunization, exerts some effect. The observations have been subject to rigid statistical scrutiny and we have no reason to doubt their accuracy.

It is difficult to suggest just what should be done about this situation but at least the indications are that certain new policies should be considered which have as their aim the lessening of the incidence of paralytic poliomyelitis by elimination of elective surgical procedures and even certain injections during epidemic times.

In summary, therefore, although I have little that is tangible to report in the way of progress in man's long struggle to prevent poliomyelitis, it is reasonable to believe that there will be progress and that it will become manifest long before the Pennsylvania Hospital celebrates its 250th Anniversary.

Exophthalmos in the Light of Current Anti-thyroid Therapy*

HENRY M. THOMAS, JR., M.D.
Baltimore, Maryland

THYROID stimulating hormone of the anterior lobe of the pituitary gland causes liberation of the hormone thyroxin from the thyroid gland, the replacement of which when of sufficient magnitude is accompanied by hypertrophy and sometimes by hyperplasia of the thyroid parenchyma.[1] In addition to this specific action it produces, possibly through the agency of other endocrine glands, transfer of fat from fat depots to the liver and striated muscles including the extraocular eye muscles.[2] It also produces round-cell infiltration in the striated musculature, which on some occasions is accompanied by inflammation such as edema, the presence of phagocytes and destruction of local tissue.[3] Thyrotropic hormone brings about these changes in the tissues of the orbit in laboratory animals in whom the thyroid gland has been removed more readily than in those in whom the thyroid gland has not been disturbed.[4] Whether or not all endocrine exophthalmos depends on the activity of the thyrotropic hormone of the pituitary gland cannot at present be stated, but a somewhat tenuous theory has been elaborated to differentiate an additional type of exophthalmos depending on changes taking place solely from the thyroid hormone in Graves' disease.[5]

According to this theory, generalized muscular weakness accompanying Graves' disease affects most severely the extraocular muscles causing loss of tone and allowing the smooth muscles of Müller and Landström under stimulation of the sympathetic nervous system to produce proptosis. The development of striking and measurable exophthalmos following a dose of ephedrine administered to a patient who had been taking very large doses of thyroxin[6] is thought to lend support to this theory. When examined microscopically, tissues from the orbit of this type of exophthalmos are said to reveal degenerative changes in the muscle bundles and nerve endings with only slight change in water and fat content and very little if any cellular infiltration. This form of exophthalmos has been termed "functional exophthalmos" and orbital vascular engorgement is held responsible.[7]

In recent years these two varieties of exophthalmos have to some extent become accepted[8] as thyrotropic (or ophthalmopathic) exophthalmos and thyrotoxic (or classic) exophthalmos.* When one tries, however, to differentiate these two forms clinically and to correlate the clinical groups with pathological changes one runs into peculiar difficulty. Under modern therapeutic techniques very few cases of hyperthyroidism come to post-mortem examination. In a large number of the necropsy cases the extraocular eye muscles and the orbital contents have not been studied. Cases of malignant exophthalmos are extremely rare but when reported with descriptions of the orbital contents the clinical notes often are incomplete and a great variety of therapeutic measures has been used.

I wish to describe a few cases which demonstrate various features of this complicated clinical syndrome.

CASE 1. (JHH No. U-50895.) W. B. was a white male fifty-eight years of age. In March, 1932, at the age of fifty-two years, he had a sudden onset of weakness and pain in his arms and legs, nervousness and insomnia. After one week he was forced to stop work, and in the course of the next three weeks lost 40 pounds in

* Since this lecture was delivered a report has been published by Mann[9] dividing endocrine exophthalmos cases clinically into three groups which might be paraphrased as those with excessive TSH in (1) primary myxedema, (2) post-hyperthyroid states (postoperative (90 per cent) or spontaneous (10 per cent) and (3) active Graves' disease. She does not include exophthalmos produced without "excess thyrotropic hormone of the pituitary."

* From the Department of Medicine, Johns Hopkins Hospital and Medical School, Baltimore, Md. A lecture delivered at the 200th Anniversary Celebration of the founding of the Pennsylvania Hospital.

spite of good appetite and the BMR was found to be +22 per cent. A nodule in the left side of the neck which had been present for six or eight months became larger. There was auricular fibrillation. In September, 1932, thyroidectomy was performed by Dr. George Shipley at the Baltimore City Hospital. Following the operation all of the symptoms improved although the weakness persisted to some extent. Two months after the operation he noticed upon looking at himself in the mirror that his eyes were beginning to bulge. This continued until four months postoperative when he developed sharp pains in the eyes and double vision. Over the course of the next six months the protrusion of the eyes increased gradually and vision became cloudy. In August, 1933, eleven months after thyroidectomy, papilledema became marked on both sides and decompression of the right orbit was performed by Dr. Walter Dandy, using the Naffziger technic of removal of the superior wall of the orbit through a craniotomy approach. The orbital fascia bulged through the opening and when this was divided fat bulged much further. The superior rectus muscle was found to be enlarged, scarred and, when observed microscopically, contained round cell infiltration. Three and one-half weeks later a similar operation was performed on the left side with identical results. Following these operations there was prompt improvement in the exophthalmos and the swelling of the disc diminished from 2 to 1 diopter and the vision improved rapidly. There was no change in the ophthalmoplegia.

Summary. In this case there was sudden onset of Graves' disease characterized by moderate hyperthyroidism with auricular fibrillation and diffuse pain and weakness of the muscles and no eye signs. Progressive exophthalmos began two months after thyroidectomy and finally orbital decompression revealed orbital contents similar to those described by Naffziger.[3]

Case II. (JHH No. 312235.) J. H. W. was a white female fifty years of age. During a period of great worry about her son this patient at the age of forty-six (1933) developed moderately active exophthalmic goiter. After rest in bed for one month and sedation there was marked improvement. At the age of forty-nine the symptoms recurred. On a regimen of half rest she remained mildly toxic but four months before admission all the symptoms became much worse, including loss of weight in spite of a huge appetite and starey eyes which were not particularly prominent. The BMR was +43 per cent. Subtotal thyroidectomy was performed by Dr. William F. Rienhoff, Jr., on October 21, 1936, with complete relief of hyperthyroid symptoms and promptly followed by a gain of 20 pounds. Three months later her eyes began to bother her with double vision, amber colored vision in the right eye and swollen eyelids particularly in the morning. The unrelated symptom of "buzzing in the ears" developed after thyroidectomy. On April 7th examination revealed the right eye movement definitely limited downward. The left eye moved down fairly well but was limited in abduction and adduction elevation was practically abolished. The right visual axis appeared to lie about 2 mm. above the left axis. Dr. Alan C. Woods diagnosed paralysis of the right depressors and left elevators. Exophthalmometer measurements were right 24 mm., left 25 mm. Thyroid extract replacement therapy was begun April 21, 1937, starting with 1 gr. daily, increasing in three weeks to 3 gr. daily, with the result that on May 17, 1937, the BMR had risen from the original −9 to +18 per cent. By suitable dosage (2½–3 gr. daily) the BMR was maintained at about this level for the next four years, being +14 per cent in November, 1938, and +15 per cent in June, 1940. The exophthalmos receded definitely during this period, measuring in November, 1938, right 19 mm., left 21 mm.; in June, 1939, right 20 mm., left 22 mm.; in June, 1940, right 20 mm., left 21 mm., and in May, 1943, right 18 mm., left 18 mm. As the exophthalmos diminished the ophthalmoplegia became more marked and presented the picture of an extreme bilateral internal strabismus.

Encouraged by the improvement under thyroid replacement therapy which was maintained over a period of years, Dr. Woods performed "Recession of the right internal rectus" with excellent therapeutic results. Examination of a small portion of the muscle near the tendon insertion, which was removed at the time of operation and after complete subsidence of Graves' disease, failed to show any abnormalities when examined microscopically.

Since that time the patient has taken small doses of thyroid extract with the idea of maintaining her basal in the neighborhood of plus or minus zero, this being ½ to ¾ gr. daily, and the eye condition has remained stationary.

Summary. This case of moderately severe

exophthalmic goiter with moderate exophthalmos was treated by subtotal thyroidectomy. Three months after operation the eyes began to protrude increasingly, measuring 25 mm. right, and 24 mm. left and ophthalmoplegia developed. Thyroid extract was given in amounts adequate to maintain the basal metabolic rate in the neighborhood of +15 per cent with gradual recession of the exophthalmos so that within a year the measurements were right 20 mm., left 21 mm., and after four years were right 18 mm., left 18 mm. Corrective operation on the eye muscles was successful and revealed normal muscle and tendon. The underlying Graves' disease has been quiescent or cured since that time.

Case III. (JHH No. 401483.) L. L. L., a colored female, age forty years, had been treated for idiopathic epilepsy in the outpatient department of The Johns Hopkins Hospital for the past four years. In April, 1950, it was noted that there were signs of mild Graves' disease and she was referred to the thyroid clinic. She failed to keep this appointment and subsequent history reveals that she returned to her home in North Carolina where subtotal thyroidectomy was performed July 13, 1950. When next seen in the Johns Hopkins outpatient department in October, 1950, she had moderate proptosis measuring 27 mm. on each side. BMR was 8 per cent. While under observation the eyes became more inflamed, there was marked lachrymation, and then the right eye became fiery red and inflamed and progressively protruded so that on October 25th it measured 33 mm., left eye 27 mm. She was put on penicillin, aureomycin and treated with cortisone 300 mg. the first day, 200 mg. the second day and 100 mg. thereafter for a total of eight days. No improvement in proptosis nor in inflammatory reaction was noted. Following this on the advice of Dr. Alan C. Woods the right orbit was decompressed by removal of a portion of the temporal bone, and a week later the left orbit was decompressed also. Before operation the patient was able only to count fingers held 3 inches before the right eye. The left eye was corrected to 20/30ths. After operation vision was 20/20 in both eyes. Tissue removed at the first operation revealed lachrymal gland with nests of round celled infiltration, and at the second operation granulation tissue with marked round celled infiltration.

Summary. This patient represents a mild case of Graves' disease with exophthalmos which, three months after subtotal thyroidectomy, became extreme in one eye. Cortisone treatment for eight days produced no improvement and bilateral orbital decompression was resorted to.

Case IV.* (JHH No. 429365.) I. M., a white male, 67 years of age, was an extremely intelligent retired Jewish business man who was admitted to the surgical service of the Johns Hopkins Hospital in September, 1947, for treatment of gastric ulcer.[11] At that time he gave a history of recently having become quite nervous, lost weight, developed tremor and that his eyes had become prominent. It is to be noted that the prominence of the eyes must have been relatively mild since this patient had been seen on several occasions by an astute surgical diagnostician. On September 25, 1947, his BMR was +72 per cent. Believing that thyroidectomy was indicated he was started, by Dr. Alan Bernstein, on strong iodin solution (Lugol's solution) 0.5 cc. three times daily and N propyl thiouracil 300 mg. daily. In two weeks the BMR had fallen to +7 per cent, and the only remaining complaint was lachrymation. Iodin was permanently discontinued. Two weeks later, on October 22nd, the test showed BMR +5 per cent, a gain of 7 pounds in weight, and it was noticed that his "eyes are extremely prominent with marked lid lag." The thyroid enlargement was noted to be minimal. Propyl thiouracil dosage was gradually reduced to 150 mg. daily, and five months after treatment was begun he had regained his average weight of 136 pounds, the BMR was +4 per cent and the eyes were reported quite prominent with marked stare and lid lag.

Approximately thirteen months after beginning N-propyl thiouracil treatment the drug was entirely discontinued with the hope that a more or less permanent remission had been effected. Within a month he noticed a recurrence of some of his hyperthyroid symptoms, particularly weakness, cramp in the right leg if he walked more than a block, tremor of the hands and a feeling as if his eyes were popping out, particularly the right one. Not until two months after discontinuing medication did he return to Dr. Bernstein for examination at which time his weight had dropped to 114 pounds, BMR has risen to +24 per cent, and "his eyes are tremendously prominent once again with a

* Dr. Alan Bernstein has kindly allowed me to report this case.

tremendous lid lag, stare, poor convergence and lack of wrinkling the forehead." Propyl thiouracil 300 mg. daily was reinstituted and within a few days he began to feel better. Two and a half months later he returned for examination; his weight was 124 pounds, BMR +1 per cent, and he had several weeks before reduced the propyl thiouracil to 200 mg. daily. All the symptoms had improved with the exception of his eyes. Examination showed tremendous chemosis and injection of the right eye which was "literally popping out." The left one was not quite so prominent. There was definite diplopia when he looked to the right because of paralysis of the right external rectus, and he could not lift his right eye above the horizontal level. On that day he was seen by the ophthalmologist, Dr. Jonas S. Friedenwald, who confirmed the limitation of motion of the right eye. He also demonstrated limitation of motion in the left eye in upward rotation, and measured the eyes with a Hertel exophthalmometer: right 22 mm., left 18 mm. Although the hyperthyroid symptoms remained under complete control, the prominence of the eyes increased so that in May, 1949, the measurements were right 26 mm., left 23 mm. On August 2, 1949, the BMR was −12 per cent. He continued taking propyl thiouracil 200 mg. daily, and on April 14, 1950, the BMR was −24 per cent; subjectively lachrymation and other eye symptoms were better and the exophthalmos had receded to right 23 mm., left 20 mm. Propyl thiouracil again was discontinued this time after a course of fifteen months. Within about four weeks he began to feel weak, to lose weight, and to have increased trouble with his eyes. Six weeks after discontinuing propyl thiouracil Dr. Friedenwald found no change in eye measurements but noted further extraocular palsies, optic neuritis and diminution of vision on the right. In order to save the vision he performed orbital decompression on the right by removal of a portion of the right temporal bone and periosteum, and one week later performed a similar operation on the left. Twelve weeks after discontinuing propyl thiouracil treatment the basal metabolism had risen to +3 per cent and he was started again on 150 mg. daily. Within a few months the BMR had fallen to −13 per cent, and the eye had remained almost normal following the operation.

Summary. This sixty-seven year old man developed severe exophthalmic goiter with slight exophthalmos which increased while the hyperthyroidism was otherwise satisfactorily and easily controlled by propyl thiouracil. When propyl thiouracil was discontinued, the disease flared up again and at this time exophthalmos and other eye symptoms became greatly aggravated. When hyperthyroidism was controlled, the proptosis continued to increase and then receded slightly. After fifteen and a half months more of treatment with propyl thiouracil producing hypothyroidism the drug again was stopped with return of the BMR from −24 to +3 per cent, but with increase in eye signs including optic neuritis and impending loss of vision in one eye. Surgical decompression of both orbits was performed with excellent therapeutic result, and on small doses of propyl thiouracil the basal metabolism remains −13 per cent and the hyperthyroidism and eye symptoms are quiescent.

COMMENTS

In 1936 we stated:[3c] "The main ideas advanced to explain the exophthalmos of Graves' disease are (1) an increase in the orbital fat, (2) edema of the normal orbital contents, (3) congestion of the vascular bed of the orbit, (4) relaxation of the extraocular eye muscles, (5) contraction of the smooth muscles of Müller, Landström, and Hesser, (6) hypertrophic myositis of the extraocular muscles."

During the past fifteen years, and I should point out that each of these ideas goes back much further than fifteen years, studies of orbital contents in patients operated on for or dying with Graves' disease, and the production of exophthalmos in laboratory animals by injection of anterior pituitary thyrotropic extract (thyroid stimulating hormone, TSH) has narrowed attention to the first two. At the moment a group in London (Rundel, Wilson and Pochin)[10] believe that ". . . exophthalmos in human Graves' disease is due largely to an increase in orbital fat." The Boston group support the thesis that edema of the various elements of the orbital contents provides the force which protrudes the eyeball forward (Means, Hertz, Rawson, Dobyns).[11] Congestion of the vascular bed of the orbit and hypertrophic myositis of the extraocular muscles while frequently occurring are considered by most people as contributing to rather than actually producing proptosis. I wish again to call attention to the type of inflammatory reaction in these muscles which is seen also throughout the fat and other orbital contents.[3a,c] There are in Graves' disease and

also in Addison's disease large collections of round cells throughout the body in muscle and some other tissues. It seems to me likely that this plays a particular role in the production of orbital edema. Dobyns[3] also has described this feature although he is more interested in fat phagocytized by large tissue macrophages and polymorphonuclear leukocytes, which cells along with many lymphocytes were seen invading the retrobulbar fat and muscle. This is similar, he states, to the picture which was seen in animals which had been given TSH. Before him, Smelzer[12] had emphasized the fact that in general the pathologic picture in the orbital contents of animals rendered exophthalmic with TSH is the same as that reported in human cases. On the other hand, Pochin[10] states that in laboratory animals "the exophthalmos studied is largely due to an increase of water in the orbit which is probably to be regarded as a generalized orbital oedema. This contrasts with exophthalmos in human Graves' disease which is due largely to an increase in orbital fat." The increased pressure that is built up in the orbit was emphasized by us when we described the extrusion of fat when the periosteum under the orbital bone is opened in these cases, and when we recorded that in another case in whom, following bilateral ennucleation of the eyes in another hospital, the orbital contents continued to increase and to bulge from the orbit requiring further surgical excision.

We know, then, what occurs to orbital contents when exophthalmos develops in man and in treated laboratory animals but we do not as yet understand the mechanism which produces proptosis. TSH of the anterior pituitary in some manner seems to be a major factor.

The influence of endocrine glands other than the pituitary was strongly indicated by Marine's[13] experiments with castration in guinea pigs which abolished exophthalmos produced by methylcyanide. In our early series we pointed out that there were eleven males and only four females in spite of the usual preponderance of women over men with hyperthyroidism. Dobyns tabulated all cases of severe progressive exophthalmos reported prior to 1950 and found eighty-one males and sixty-four females; and of the very severe cases who require radical treatment forty-four of sixty-five, or 67.7 per cent, were males.

The unanswered questions to date are: Does thyrotropin (TSH) play *the* active role in the production of exophthalmos in human cases; and if so, how does it exert this influence? Similar questions may be asked about ophthalmoplegia which usually involves the superior rectus extraocular eye muscle but may involve any or all of the other muscles, and which may occur with or without exophthalmos or lid retraction. On the other hand, advanced exophthalmos may be seen with no ophthalmoplegia. In Means' ophthalmopathic form there is ophthalmoplegia and severe edema of the orbital and palpebral tissues. Here again, the exact mechanism of the extraocular eye muscle paralysis is not clear, but pathologic changes in the muscles with involvement of the nerve end-organs which might be produced by the inflammatory reaction including the round cell infiltration, supply a probable solution.

Clinical study of cases of progressive exophthalmos demonstrated the fact that exophthalmos increases markedly some months to years after thyroidectomy often when the metabolic rate has fallen to subnormal levels. It has been shown that exophthalmos is produced more readily in guinea pigs following the removal of the thyroid gland. Thyrotropic substances were found in the urine of patients with myxedema,[14] a small amount in normal persons and none at all in thyrotoxic patients. Later Raulson demonstrated that inactivated thyroid stimulating hormone was present in large amounts in the urine of thyrotoxic patients, and this substance could be activated by heating. He further demonstrated that normal thyroid tissue slices are capable of neutralizing TSH 1 unit per mg. whereas thyroid tissue slices from Graves' disease neutralize 5 to 10 times as much TSH. This lead to the belief that the normal thyroid gland and, to a greater extent, the hyperplastic thyroid gland is capable of inactivating thyrotropin. Everything points, therefore, to an excess of non-inactivated thyrotropin as a necessary feature of endocrine exophthalmos; and in those cases in which thyrotropin is secreted by the pituitary in large amounts, removal of the thyroid gland with its power to neutralize thyrotropin leads to the production or increase of already present exophthalmos.

On the basis of unfortunate clinical experiences and the elaborate network of laboratory discoveries every effort should be made to avoid thyroidectomy in the "ophthalmopathic form." It is equally clear, however, that many cases of this form cannot be differentiated before the process leading to progressive exophthalmos is

put into action. More than slight edema of the eyelids should be a warning.

Case IV of this series introduces a new observation to be considered. Here the original mild exophthalmos increased during propyl thiouracil treatment. Dobyns and others have reported single cases which have developed severe progressive exophthalmos during adequate treatment with propyl thiouracil. Then when the propyl thiouracil was discontinued after a year the basic hyperthyroidism emerged and with it a startling increase in proptosis. When propyl thiouracil was again in command of the hyperthyroidism the proptosis continued to increase and then slightly to wane. Fifteen months later propyl thiouracil again was discontinued and as the subnormal BMR rose to normal the eye signs again increased, this time to include optic neuritis in one eye.

To incorporate these facts into the current concept of thyrotropic exophthalmos one must conclude that the moderately overactive thyroid gland is less capable of inactivating thyrotropin than is the gland completely blocked but hypertrophic and hyperplastic under the influence of propyl thiouracil. Cases developing exophthalmos during propyl thiouracil treatment constitute a small percentage in which the stimulated production of thyrotropin is excessive and in such cases discontinuance of propyl thiouracil precipitates a critical state.

There is another feature which has, as yet, not been elucidated. In each situation in which exophthalmos is known to progress there seems to be a relative lack of body iodin in comparison to the amount of thyrotropic hormone. The body iodin unless utilized in the cycle of thyroid metabolism gradually is excreted as is the small amount of iodin daily ingested in food. Thus in cases of myxedema or cases adequately or excessively treated with propyl thiouracil little or no stored iodin is available when the thyroid gland is unblocked and synthesis of thyroxin again is undertaken. Thyrotropic hormone given to myxedematous animals produces exophthalmos whereas dessicated thyroid gland containing fully synthesized thyroxin produces a reduction in the proptosis of myxedema. In cases of severe Graves' disease with exophthalmos the symptoms subside when the iodin supply is made adequate. It may be suggested, therefore, that a necessary factor in the production of progressive exophthalmos is a previously deficient supply of available iodin, although coincident administration of sodium iodide does not affect exophthalmos produced in guinea pigs by injection of anterior pituitary extract.[15]

CONCLUSIONS

1. Four cases of Graves' disease illustrating various degrees and modes of onset of progressive exophthalmos and ophthalmoplegia have been presented.

2. A liberal amount of thyrotropic hormone which has not been inactivated seems to be an essential factor in cases of severe exophthalmos.

3. The rapid development of dangerous exophthalmos occurring in a case which was allowed to escape the restraining influence of propyl thiouracil on two occasions has been described.

4. The possibility that a relatively deficient iodin store plays a role in endocrine exophthalmos has been suggested.

REFERENCES

1*a*. Smith, P. E. and Smith, I. P. The repair and activation of the thyroid in the hypophysectomized tadpole by the parenteral administration of fresh anterior lobe of the bovine hypophysis. *J. M. Research*, 43: 267, 1922. (*b*) Loeb, L. Studies on compensatory hypertrophy of the thyroid gland. VIII. A comparison between the effect of administration of thyroxin, thyroid and anterior pituitary substance on the compensatory hypertrophy of the thyroid gland in the guinea pig. *Am. J. Path.*, 5: 71, 1929. (*c*) Aron, M. Action de la prehypophyse sur la thyroide chez le cobaye. *Compt. rend. Soc. de biol.*, 102: 682, 1929. (*d*) De Robertis, E. Cytological and cytochemical bases of thyroid function. *Ann. New York Acad. Sc.*, 50: 317, 1948–50.

2*a*. Smelser, G. K. A comparative study of experimental and clinical exophthalmos. *Am. J. Ophth.*, 20: 1189–1203, 1937. (*b*) Paulson, D. L. Experimental exophthalmos in guinea pigs. *Proc. Soc. Exper. Biol. & Med.*, 36: 604–605, 1937. (*c*) Aird, R. B. Experimental exophthalmos and associated myopathy induced by thyrotropic extract. *Arch. Ophth.*, 24: 1167–1178, 1940; *Ann. Int. Med.*, 15: 564–581, 1941. (*d*) Dobyns, B. M. Studies on exophthalmos produced by thyrotropic hormone. II. Changes induced in various tissues and organs (including the orbit) by thyrotropic hormone and their relationship to exophthalmos. *Surg., Gynec. & Obst.*, 82: 609–617, 1946.

3*a*. Naffziger, H. C. Progressive exophthalmos following thyroidectomy; its pathology and treatment. *Ann. Surg.*, 94: 582–586, 1932. (*b*) Friedenwald, J. S. Orbital myositis and choked disc in exophthalmic goiter. *Ann. Surg.*, 96: 995, 1932. (*c*) Thomas, H. M., Jr. and Woods, A. C. Progressive exophthalmos following thyroidectomy. *Bull. Johns Hopkins Hosp.*, 59: 99–113, 1936. (*d*) Dobyns,

B. M. Present concepts of the pathologic physiology of exophthalmos. *J. Clin. Endocrinol.*, 10: 1202–1230, 1950.

4*a*. Marine, D. and Rosen, S. H. Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary, and the mechanism involved. *Proc. Soc. Exper. Biol. & Med.*, 30: 901, 1933. (*b*) Smelser, G. K. Experimental production of exophthalmos resembling that found in Graves' disease. *Proc. Soc. Exper. Biol. & Med.*, 35: 128–130, 1936.

5. Mulvaney, J. H. The exophthalmos of hyperthyroidism. *Am. J. Ophth.*, 27: 589, 693, 820, 1944.

6. Labbe, M., Villaret, M., Justin-Besançon, L. and Schiff-Wertheimer. Récherches sur la pathogénie de l'exophthalmie basedowienne et son traitement. *Bull. Acad. de méd., Paris*, 110: 730, 1933.

7. Friedenwald, J. S. Personal communication.

8. Woods, A. C. The ocular changes of primary diffuse toxic goitre: a review. *Medicine*, 25: 113–153, 1946.

9. Mann, I. A further report on exophthalmic ophthalmoplegia and its relations to thyrotoxicosis. *Am. J. Ophth.*, 34: 960–976, 1951.

10*a*. Rundle, F. F. and Wilson, C. W. Bulging of eyelids with exophthalmos. *Clin. Sc.*, 5: 31–49, 1944. (*b*) Rundle, F. F. and Pochin, E. E. The orbital tissues in thyrotoxicosis: a quantitative analysis relating to exophthalmos. *Clin. Sc.*, 5: 51–74, 1944.

11*a*. Hertz, S., Means, J. H. and Williams, R. H. Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy. *West. J. Surg.*, 49: 493–498, 1941. (*b*) Rawson, R. W., Hertz, S. and Means, J. H. Cyanate goiter in man. Report of a case with histological and metabolic studies. *J. Clin. Investigation*, 21: 624, 1942.

12. Smelzer, G. K. Experimental production of exophthalmos resembling that found in Graves' disease. *Proc. Soc. Exper. Biol. & Med.*, 35: 128–130, 1936.

13. Marine, D. Studies on the pathological physiology of the exophthalmos of Graves' disease. *Ann. Int. Med.*, 12: 443, 1938.

14. Rawson, R. W. Quoted by Means, J. H. The nature of Graves' disease with special reference to its ophthalmic component. *Am. J. M. Sc.*, 207; 1, 1944.

15. Smelzer, G. K. Treatment of experimentally produced exophthalmos with thyroxin and other iodin compounds. *Am. J. Ophth.*, 21: 1208, 1938.

The Place of Psychiatry in Medicine

E. D. Bond, M.D.

Philadelphia, Pennsylvania

There is an understanding that the task of any medical specialty is twofold: it must pursue the most intricate investigations in its own field and then bring back to the main body of physicians those findings which are plain, definite and widely useful.

Psychiatry is working in its own field through psychoanalysis, experimental management of the interview, insulin and electric shock therapies, group therapy, genetic studies especially of identical twins, and other methods. It must keep alert to new knowledge of the anatomy and physiology of the nervous systems. Some practitioners in this field in order to do good work must cut themselves off from other kinds of medicine and indeed from the usual participation in community life. They live in their ivory towers by necessity but fortunately information about their discoveries can reach the outside world, often through the mediation of other less specialized psychiatrists who can keep in touch with the medical community.

There are two aspects of this information which are important to the general practise of medicine:

1. Psychiatrists are piling up evidence that emotions are factors in the diagnosis, treatment and prognosis of the disease of all organs of the body. The idea is not a new one. Dr. Padis, in a recent paper before the College of Physicians, quoted Plato: "Whenever the soul. . . . is in a passionate state, it shakes up the whole body from within and fills it with maladies." Physiologists have shown that it is the mediation of the autonomic nervous system and the blood which bring about changes in the function of organs. Their controlled experiments are convincing. In fact, the general physician has accepted the power of the emotions as true in physiology but not applicable to his daily practice.

In this attitude the physician has been abetted by his clinical journals which avoid the word "emotion" as if it were not a scientific term. Here are sentences from recent publications: "The reduction in the secretion produced by complete division of the vagus nerves to the stomach proves that the hypersecretion is neurogenic in character." This seems to suggest that there is a lesion part way up the vagus nerves. The psychiatrist suggests following through to the real origin of the disturbance—to such an emotion as the anger a man felt when he discovered that a trusted partner had cheated him. Notice also the phrases in a late and good article. "The hypersecretion—is chiefly, if not exclusively, of nervous origin and is abolished by vagotomy"; "implicating the central nervous system"; "the tension and strain of modern life." There is apparent avoidance of the physiological terms "emotion and the autonomic nervous system."

2. Into the clinical picture the psychiatrist often or usually brings a second person. This meets with understandable objection from many busy physicians: "Isn't one body complicated enough? Why must a second be brought in"? But it was a physiologist, Walter Cannon, who brought in a second person to explain a gastric analysis which showed lack of secretion. The patient had been brought to Boston the day before the analysis and her husband had drowned his anxiety by getting drunk and creating a scene of which the patient was deeply ashamed. On another day, with the second person behaving well, plenty of secretion was present.

Out of an interest in these two overlapping aspects of the clinical picture—the emotions and the second person who can cause them—comes a view of the patient as a whole person. The psychiatrist is ashamed that in large mental hospitals the individual is lost in a crowd; he is afraid that in general hospitals the growing excellence of investigational procedures which tell so much about every organ may keep a busy physician out of touch with the whole patient and his responses to people about him. More and more the total personality is being recognized, and the following extensions of psychiatric thinking into medicine are noteworthy.

Cardiologists report that in spite of the enor-

mous and growing incidence of cardiovascular disease the majority of patients who have symptoms referred to the heart region do not have organic heart disease. Emotions which make a heart light or heavy account for the symptoms of this majority. Anxiety and fear use the heart as their end organ.

Gastroenterologists often find about half of their cases functional. Some describe their puzzling patients as "intellectual, neurotic or tense," a curious commentary on "intellectuals." Dermatologists find emotional factors in urticarias, eczemas and other diseases. Surgeons are interested in the meanings of pain, and emotions can cause pain.

Pediatricians find more sudden and violent body responses to emotions in children than in adults. If this morning we could have looked into the homes of school children all over the country at about 8 A.M., we should have found thousands of headaches, digestive upsets, pains which subsided after 9 A.M., most of them the result of fear of what would happen in school or on the way. And just as a pediatrician or family doctor might well take into his diagnosis the emotions that might in a school child be centered upon 9 A.M., so any doctor in any diagnosis is better equipped if he knows what zero hour his patient is facing.

"Doctor, I hope you find something wrong with every gland in my body for it will postpone the fateful decision I have to make!"

Here are suggestions that psychiatrists bring back from their own studies of tangled loves and hates: (1) If symptoms hang together to make a clear diagnosis in a reasonable time, regard emotional factors as minor or negligible. (2) When symptoms are not in step, when they are inconsistent and fluctuating, give emotional factors an even chance with those physical.

When these suggestions are neglected, a letter such as the following can come from a surgical to a psychiatric service. "We are referring a woman of 40. Because of a complaint of questionable pain she has had four operations and much novocaine. After two years and because of the recurrent complaint regardless of treatment we are referring her to you with the diagnosis of psycho-neurosis." This is locking the barn door after the horse was stolen. But when physicians, surgeons and specialists give emotional factors an even chance early in doubtful cases, they are surpassing psychiatrists in the cure of budding neuroses and they are making diagnoses which are a credit to medicine. They are recognizing that any organ in the body can become the loud-speaker for strong emotion.

These good results come not from the application of special psychiatric technics but from the change in an attitude of the physician who has recognized the prevailing emotion in a patient and looked for the person who caused it. One internist takes an hour and a half for the first interview and thinks that this saves him time later.

Psychiatry's place in medicine does not stand on psychosomatics alone. In its own field it is discovering and relieving "the exquisite forgotten agonies of childhood," the deeper origins of prejudice and hostility and unreason. These are contributions to the total health of man, the goal of all medicine.

End of Anniversary Papers

Review

Hemochromatosis*

ALEXANDER MARBLE, M.D. *and* C. CABELL BAILEY, M.D.
Boston, Massachusetts

SINCE 1922 thirty cases of proven and seventeen cases of probable hemochromatosis with diabetes have been recognized in this clinic. Although the condition is not rare, it is certainly uncommon and a relatively small number of cases has been reported in the American literature. As a matter of fact, when Sheldon wrote his monograph on hemochromatosis published in 1935,[1] an exhaustive search of the world literature revealed only 345 cases. Of these he excluded thirty-four from consideration because of insufficient evidence supporting the diagnosis. Undoubtedly, the number of published cases does not afford an accurate indication of the incidence of hemochromatosis since the files of many laboratories of pathology contain unpublished records.

Our cases of hemochromatosis are reported not only because of the infrequency of the disease but also because of the following considerations: (1) Most of the patients in our series have been followed up closely over years of time thus providing good opportunity for observing the course of the disease. (2) Three of the patients were women; hemochromatosis is rare in females. (3) Three of the patients are living with duration of diabetes to January, 1951, of 13.0, 8.8 and 5.7 years, respectively, reflecting the increased length of life now possible. (4) The series includes two especially noteworthy cases, namely, a patient (Case 6247) reported in detail previously[2] who died in diabetic coma despite having received 1,600 units of insulin daily for the three days prior to death, and a patient (Case 12069) whose diabetes was of 17.6 years' duration at the time of death and whose iron metabolism was studied in detail and reported elsewhere.[3]

The thirty cases of proven hemochromatosis are those in which the diagnosis has been confirmed histologically by skin biopsy, autopsy or both. The seventeen probable cases are those seen in this clinic in the last twenty-eight years which have shown enlargement of the liver, pigmentation of the skin and diabetes, together with some of the other symptoms and signs characteristic of hemochromatosis, but in which confirmation of diagnosis has not been possible by histologic means. The total of forty-seven cases recognized represents an incidence of about 0.16 per cent among approximately 30,000 new cases of diabetes mellitus seen in this clinic since 1922.

DIAGNOSIS OF HEMOCHROMATOSIS

The diagnosis of hemochromatosis may be suspected clinically when the triad of skin pigmentation, cirrhosis of the liver and diabetes mellitus is present. Evidence of gonadal hypoplasia lends weight to the diagnosis. A positive diagnosis depends upon the finding of hemosiderin in tissues obtained at skin biopsy, liver biopsy, bone marrow aspiration or autopsy. Three other procedures have been advocated, namely, (1) examination of the urinary sediment for intracellular hemosiderin, (2) the injection of acidified potassium ferrocyanide intradermally as suggested by Fishback[4] and (3) the demonstration of an abnormally high serum iron with a high percentage saturation of the iron-binding protein.[5]

Aside from the examination of multiple tissues at post mortem the most conclusive procedure is study of material removed at liver biopsy. However, this is often not possible or desirable and an easier although less reliable method is the examination of a bit of excised skin for evidence of iron deposits. A small portion of excised skin is placed in alcohol-formalin, imbedded in colloidin, sectioned and stained for iron with potassium ferrocyanide by Mallory's method and counterstained with basic fuchsin. The presence of hemosiderin may be demonstrated

* From the George F. Baker Clinic, New England Deaconess Hospital, Boston, Mass.

in the corium especially in the cells of the sweat glands, in the connective tissue cells and the endothelium of the capillaries and smaller blood vessels. The epidermis in some cases may show deposits of hemosiderin in the cells of the basal layers although an increase in melanin alone is the characteristic finding.

Although in our experience not so trustworthy as other procedures, the demonstration of hemosiderin in the cells of the urinary sediment (epithelium of bladder wall, ureters or kidney pelvis) as described by Rous[6] may be helpful in diagnosis. The method is as follows:

A fresh specimen of urine is centrifuged and the sediment suspended in 10 cc. of a fresh mixture containing equal parts of 2 per cent potassium ferrocyanide and 1 per cent hydrochloric acid. After standing for ten minutes this is centrifuged and a drop of 1 per cent hydrochloric acid is added to a drop of the sediment on a slide. Blue intracellular granules indicate the presence of iron.

Less satisfactory in our limited experience has been the intradermal test suggested by Fishback. In fact, in certain cases of proven hemochromatosis the intradermal test has been negative. Furthermore, in one patient a slightly deeper injection (into the corium) was likewise negative.

A mixture is made of equal parts of N/100 hydrochloric acid and 0.5 per cent potassium ferrocyanide. Of this, 0.1 cc. is injected intradermally. If significant amounts of iron are present, a deep blue color appears at the site of injection almost immediately. The mixture should be handled aseptically but cannot be sterilized by heat.

Rath and Finch[5] found that the serum iron averaged 224 gamma per 100 cc. in nine cases of hemochromatosis as compared with a control value in normal individuals of 100 gamma per 100 cc. Furthermore, although the iron-binding capacity of the plasma protein in hemochromatosis averaged about 200 gamma as compared with a normal of 300 gamma per 100 cc., this capacity was saturated to the extent of 91 per cent in the patients with hemochromatosis as compared with the normal of 34 per cent. Thus in hemochromatosis the serum iron is elevated and, although the iron-binding capacity of the plasma protein is less than normal, this capacity is almost completely filled. Experience to date suggests that these determinations may be of distinct value in the diagnosis of hemochromatosis. It is of interest that qualitatively similar results have been noted in certain apparently healthy relatives of patients with hemochromatosis.

As early as 1897 Jeanselme[7] reported that sections of liver removed post mortem from a patient with hemochromatosis showed increased density by roentgenogram. This fact had received scant attention until Sosman and associates[8] detected on an abdominal x-ray film an increase in liver density and a double contour line along the diaphragmatic border in a patient later proved to have hemochromatosis. Following this, in a review of films of eleven patients with hemochromatosis at the Peter Bent Brigham Hospital, they found an increase in liver density in nine of ten patients of whom roentgenograms of the abdomen had been taken. Further experience will be necessary to determine the reliability of this proposed diagnostic aid.

CLINICAL FINDINGS IN THIRTY PROVEN CASES

The outstanding features regarding the thirty proven cases of hemochromatosis are presented in Table 1. Of these, twenty-seven have died; in fifteen a postmortem examination was carried out and the diagnosis verified. In each of the thirty cases the diagnosis was made on the basis of enlarged liver, diabetes and the demonstration of hemosiderin in tissues removed at biopsy or autopsy. Twenty-five of the thirty cases revealed characteristic pigmentation of the skin.

Sex. Of the thirty cases three were females. Two of the women have died and in one case an autopsy was allowed while in the other a skin biopsy confirmed the diagnosis. The extreme rarity of hemochromatosis among women makes these three patients of especial interest. Sheldon recognized only thirteen cases among a total of 311 cases in the literature.

Duration of Diabetes. The age at onset of diabetes among the thirty patients ranged from 36.7 to 78.1 years with an average of 52.9 years. However, in only one case was the onset of diabetes below the age of forty and in twenty-three patients it was between the ages of forty-five and sixty years. Among the fatal cases the average age at death was 57.8 years, representing in this group a remarkably short average duration of diabetes of 4.9 years. Of the three living cases the average age at the present time (January, 1951) is 64.0 years with an average duration of diabetes to date of 9.2 years.

Severity of Diabetes. The severity of the diabetes varied considerably from patient to patient. In general the insulin requirement was

TABLE I

SUMMARY OF CLINICAL FINDINGS IN THIRTY CASES OF HEMOCHROMATOSIS

No.	Case No.	Sex	Age, Onset of Diabetes	Age at Death	Duration Diabetes (Yr.)	Maximum Insulin Daily	Diabetes Heredity	Alcohol	Signs and Symptoms							Skin Biopsy	Cause of Death	Autopsy
									Weakness	Loss of Weight	Abdominal Pain	Skin Pigmentation	Hepatomegaly	Splenomegaly	Ascites			
1	2693	M	45	49	4	0	+	0	+	+	0	+	+	+	+	Positive	Pneumonia	0
2	6247	M	55	56	1	1,600	0	0	+	+	+	0	+	+	0	None	Diabetic coma	+
3	7400	M	58	61	3	75	0	0	+	+	0	0	+	0	0	Positive	Pneumonia	0
4	7474	M	60	61	1	23	0	Occasional	+	+	0	0	+	+	0	None	Coronary thrombosis	+
5	9035	F	52	54	2	114	0	No data	+	+	0	+	+	+	+	Negative	Coronary Insufficiency	+
6	9219	M	48	49	<1	270	0	Rare	+	+	+	+	+	+	+	Positive	Coronary thrombosis	0
7	9749	M	49	56	7	39	+	0	+	+	+	+	+	+	0	Positive	Hemochromatosis	+
8	10093	M	58	59	1	30	+	Rare	+	+	+	+	+	0	0	Negative	Lobar pneumonia	+
9	10671	F	53	56	2	105	0	0	+	+	+	+	+	+	0	Positive	Hemochromatosis	0
10	10756	M	56	58	2	21	0	0	+	+	+	+	+	0	+	Negative	Ruptured esophageal varix	+
11	11167	M	55	55	<1	30	0	0	+	+	+	0	+	+	+	None	Peritonitis	+
12	12069	M	45	62	17	48	+	Occasional	+	+	0	+	+	+	0	Positive	Carcinoma liver	+
13	12120	M	51	51	<1	27	0	Moderate	+	+	+	+	+	0	0	Positive	Hemochromatosis	0
14	12225	M	43	43	<1	56	+	Moderate	+	+	+	+	+	+	+	Positive	Hemochromatosis	+
15	12603	M	58	59	<1	147	0	0	+	+	0	+	+	+	0	Positive	Hemochromatosis	0
16	13775	M	55	66	11	52	0	0	+	+	0	+	+	+	0	Positive	Coronary Insufficiency	0
17	14574	M	36	39	3	80	0	Rare	+	+	0	+	+	+	0	Positive	Hemochromatosis	0
18	15560	M	56	58	2	54	+	Occasional	+	+	0	+	+	0	0	Positive	Hemochromatosis	0
19	17773	M	53	58	5	48	0	0	+	+	0	+	+	+	+	Positive	Hemochromatosis	+
20	22158	M	47	Alive	*	210	0	Moderate	+	+	0	+	+	0	0	Positive	Alive	−
21	4658	M	41	58	17	42	0	Moderate	+	+	0	+	+	+	+	Positive	Hemochromatosis	0
22	26597	M	45	53	7	80	0	0	+	+	+	+	+	+	+	Positive	Congestive heart failure	+
23	21056	M	45	49	4	36	0	0	+	+	+	0	+	+	0	Negative	Hemochromatosis	+
24	27587	M	65	70	5	36	+	0	+	+	0	+	+	+	+	Positive	Bronchopneumonia	0
25	28576	F	56	Alive	*	80	0	0	+	+	0	+	+	+	0	Positive	Alive	−
26	29487	M	60	Alive	*	24	+	+	+	+	0	+	+	+	0	Positive	Alive	−
27	8433	M	43	67	24	34	+	0	+	+	0	0	+	+	0	Positive	Coronary thrombosis	0
28	20157	M	56	58	2	12	+	+	+	+	0	+	+	+	+	Negative	Hemochromatosis	+
29	33047	M	55	63	8	25	+	Moderate	+	+	0	+	+	+	0	Liver biopsy	Carcinoma liver	+
30	18816	M	78	79	1	14	+	Occasional	+	+	0	+	+	+	+	Negative	Carcinoma liver	+

* In Cases 20, 25 and 26 the patients were alive January, 1951, with duration of diabetes of 8.8, 13.0 and 5.7 years, respectively.

somewhat greater than that of most diabetic patients, averaging 62 units per day as a maximum dose (excluding Case 6247 described later.) Six patients at one time or another received 100 or more units daily and only one patient needed no insulin. Outstanding in his insulin requirement was Case 6247 reported by Root.[2] This patient, a physician, when studied at the New England Deaconess Hospital in August, 1927, showed much sugar and diacetic acid in the urine despite receiving from 50 to 100 units of insulin daily. Following this, at his home the amount of insulin given was gradually increased until in the three days prior to the day of death in coma on October 30, 1927, 1,600 units were administered daily. It is noteworthy that in this patient there was no abnormal pigmentation of the skin and the diagnosis was not made until the postmortem examination.

Duration of Hemochromatosis. The onset of signs or symptoms suggesting hemochromatosis (except those related to the diabetes) was usually so indefinite that no date of any significance could be assigned.

Etiologic Factors. Occupation: The occupations of the patients were very varied. Their diverse character indicates the impossibility of relating the occurrence of hemochromatosis to environmental factors such as exposure to unusual amounts of chemicals.

Heredity: In twelve of the thirty cases diabetes was known to have occurred in some relative. In no case was there any family history suggesting hemochromatosis.

Alcohol: Seven patients had consumed alcoholic beverages rarely or occasionally, whereas seven had taken moderate or large amounts. Sixteen of the thirty patients were total abstainers. It would appear that alcohol is at least not an important factor in the origin of hemochromatosis.

Symptoms and Signs. All of the thirty patients complained at one time or another of weakness and loss of weight. The cause of these symptoms was often difficult to ascertain because of the various factors concerned. In some, uncontrolled diabetes may at times have been responsible and in others, cirrhosis of the liver may have been the cause.

Abdominal discomfort was a complaint in eleven or 37 per cent of the patients. This was evidenced in some as definite pain in the right upper quadrant. In others the discomfort was generalized and at times due apparently to distention of the abdomen with ascitic fluid. The causes of the abdominal pain noted in certain patients with hemochromatosis have been discussed by Desforges.[9] He lists as possibilities adrenal cortical insufficiency, congestive heart failure, liver failure, pancreatitis, vasospasm and large bowel spasm. However, one may well question whether there is any type of abdominal discomfort characteristic of hemochromatosis.

The characteristic grayish brown, slate-colored or bronze pigmentation of the skin was noted in twenty-four cases. The degree of pigmentation varied from that in six patients in whom during life no unusual discoloration was evident but in whom autopsy disclosed hemochromatosis to that in most patients in whom the pigmentation was quite striking. The pigmentation was generalized but most intense in the axillas, groins, about the genitalia and perineum, and over the face and hands or other parts of the body exposed to the sun. Apparently, the onset of the unusual pigmentation of the skin was sufficiently gradual that a patient and his family often were unaware that a change had taken place. It was usually impossible to date with any semblance of accuracy the onset of pigmentation.

Although no pigmentation of the buccal mucous membranes was recorded in our cases, our data in this respect are incomplete. However, in his review of cases in the literature Sheldon[1] found pigmentation of the mucous membranes of the mouth reported in 16.7 per cent of 197 patients. From this he concludes that the presence or absence of pigmentation of the buccal mucosa is not a reliable guide in the differential diagnosis between hemochromatosis and Addison's disease.

Hepatomegaly occurred in all patients. The edge of the liver could be felt to descend on inspiration several centimeters and often in the mid-clavicular line to the level of the umbilicus. The edge was usually firm, non-tender and sharp; the surface of the organ in some patients seemed smooth and in others nodular.

Splenomegaly was somewhat less frequent, occurring in twenty-four of the thirty patients. In twelve patients there was ascites which appeared usually toward the end of life. In certain patients repeated paracenteses were necessary in order to remove large quantities of fluid. In most cases the fluid was clear and straw-colored. One patient died because of ruptured eosophageal varices; the true incidence of varices in this series is unknown since careful roentgenologic studies were not made routinely.

Evidences of sexual hypoplasia were common in those patients who were studied with this in mind. Unfortunately, most of the earlier patients were not so studied and hence no statement regarding incidence is possible. However, in males with hemochromatosis seen in recent years impotence and loss of libido were frequent complaints. Correlated with this was the frequent finding of thinning and loss of axillary and pubic hair, softening and atrophy of the testes and marked diminution in the size of the prostate. The decreased excretion of 17-ketosteroids in the urine found in each of six patients in whom determinations were made may have been due in part to gonadal hypoplasia and in part to diminished liver function.

Liver Function. It is difficult to summarize the data regarding liver function since the information was gathered over years of time at various stages in the development of hemochromatosis. In earlier cases there was no systematic study of hepatic function. In patients seen in later years the tests included blood bilirubin, icterus index, urine urobilinogen, serum cholesterol, serum protein and its fractions, bromsulfalein retention, thymol turbidity and cephalin flocculation tests. However, by no means were all tests carried out in all cases and in some instances data are lacking or fragmentary.

An over-all appraisal of the information available indicates that, as might be expected, marked enlargement of the liver and well advanced hemochromatosis may be present with surprisingly little indication of diminished liver function as shown in the usual tests. Thus in Case 12069 studied from 1933 until death in 1948, slight icterus with increase in blood bilirubin to 1.1 mg. per 100 cc. did not take place until the month of death. In this patient the total serum protein was not observed to be as low as 5.0 gm. per 100 cc. (albumin, 3.8; globulin, 1.2) until February, 1947, one and one-half years before death. Even at this time the bromsulfalein test gave entirely normal findings with retention of only 3 per cent of the dye at forty-five minutes (5 mg. per kg. dose). In Case 12225 who died on February 15, 1934, there was no retention of bromsulfalein at thirty minutes (2 mg. per kg. dose) in a test done twelve days before. At postmortem examination the pathologist made the following note regarding the marked changes seen in the microscopic examination of the 2,000 gm. liver: "There is a large amount of periportal fibrosis replacing the greater part of liver tissue. Remainder of liver cells are partially or completely filled with pigment. There is some necrosis of liver cells." Case 21056 who died on February 28, 1946, showed a bromsulfalein retention of only 9 per cent at forty-five minutes (5 mg. per kg. dose) in a test done five months earlier. On the other hand, Case 20157 who died on November 3, 1942, gave evidence of marked liver disturbance fourteen months prior to death. On September 13, 1941, the blood bilirubin was 1.2 mg. per 100 cc. and the bromsulfalein test (5 mg. per kg. dose) showed a 60 per cent retention in thirty minutes and 50 per cent retention in seventy minutes.

Course and Causes of Death. Despite improvement in treatment in recent years the outlook for the patient with hemochromatosis is still not good. This is due to the fact that the primary defect in the disease is still poorly understood and therefore the application of specific measures in prevention and treatment is not possible. The average duration of diabetes in the fatal cases, 4.9 years, is remarkably short. However, it is noteworthy that Case 12069 carried on for 17.6 years and Case 13775 for 11.0 years after the onset of diabetes. It is true that these patients were in far from robust health but the fact that they lived so long is extraordinary. Moreover, Case 28576 was living on January 1, 1951, with a duration of diabetes of 13.0 years. Formerly most patients with hemochromatosis died of diabetes in coma. Now, however, this part of the disease can be adequately controlled. The causes of death in the twenty-seven fatal cases were recorded as follows: Pneumonia four, diabetic coma one, cardiac six, rupture of varices one, peritonitis one, cancer of liver three and hemochromatosis eleven.

In only five of the patients listed as dying from hemochromatosis was an autopsy performed so that in these the terminal event is not definitely known. In the five in whom autopsy was permitted cirrhosis of the liver seemed to be the chief cause of death in four and possibly in all cases.

PATHOLOGIC FINDINGS

The characteristic pathologic change in hemochromatosis is a deposition of hemosiderin intracellularly which may in turn produce cellular destruction with replacement by fibrous tissue. This process is most striking in the liver, skin and pancreas, thereby producing the triad of

cirrhosis of the liver, pigmentation of the skin and diabetes. The findings in the fifteen patients in whom an autopsy was carried out are described herein.

Liver. The liver was usually enlarged, averaging 2,113 gm. in thirteen cases in which weights were available. In nine the weight exceeded 1,800 gm., two weighed 1,550 and 1,560, respectively, and one was small weighing 880 gm. The latter showed mild hemochromatosis. Grossly the liver was firm and usually finely nodular or granular. It cut with increased resistance and revealed a dark brown or reddish brown color. A marked increase in fibrous tissue was apparent presenting a periportal type of fibrosis. The capsule was often thickened. On microscopic examination a marked periportal fibrosis was found in nearly every case. A striking deposition of golden brown pigment was present. The liver cells were often engorged with pigment which on staining revealed hemosiderin and, when looked for, hemofuscin. Pigment was found also in fibrous tissue, Kupffer cells, liver capsule and in the bile duct epithelium. In three cases primary carcinoma of the liver was present, an incidence of 20 per cent among fifteen autopsied cases. Detailed findings in these three and certain other patients with hemochromatosis and carcinoma of the liver have been reported separately by Drake.[10]

Pancreas. The pancreas appeared deep brown in color and was usually of normal size. The average weight of seven pancreases in our series was 71 gm. excluding one which weighed 180 gm. The pancreatic tissue at times was partially or markedly replaced with fatty infiltration. Microscopically, there was a marked increase in interacinar and interlobar fibrosis which replaced acinar and islet tissue and produced cirrhosis of the pancreas. The golden brown pigment, hemosiderin, was deposited in large amounts in the acinar tissue, macrophages, islet cells, fibrous tissue and at times in duct epithelial cells. The islets of Langerhans were decreased in number and were frequently pigmented or atrophied. The apparent former sites of many were replaced by fibrous tissue.

Spleen. The average weight of the spleen in thirteen cases was 303 gm.; however, in only four cases did the weight exceed 300 gm. In ten of thirteen cases the organ was enlarged weighing 200 gm. or more. In most cases a perisplenitis with thickened fibrous capsule was found. The pulp showed considerable venous congestion and often an increase in fibrous tissue; this type of change has been attributed to portal obstruction secondary to cirrhosis of the liver.[1] Microscopically, yellowish brown pigment was found scattered in moderate amounts in the fibrous capsule, in reticuloendothelial cells, macrophages and occasionally in blood vessel walls.

Skin. In certain cases sections of the skin as well as those of other tissues were examined carefully by Drake.[10] A summary of his impression is as follows: "The chief diagnostic change consisted of scanty deposits of hemosiderin contained in macrophages scattered in the upper corium and in the *membrana propria* of the sweat glands. In a few instances melanin was increased in the basal layer of the epidermis. Hemosiderin deposition in the skin was never excessive histologically even in cases of severe hepatic pigmentation and absolute correlation between the degree of skin pigmentation and visceral pigmentation was lacking." Sheldon[1] describes a great increase in melanin in the deeper layers of the epidermis and in some cases hemosiderin in the cells of the basal layer. He further states that hemofuscin was confined to an occasional deposit in blood vessel walls.

Heart. The average weight of twelve hearts was 361 gm. Usually the heart muscle had a deep brown or reddish brown color. Coronary sclerosis was found in seven of fifteen cases and at times was extreme. Microscopically, specific pigment granules were noted in the muscle fibers in ten of fifteen cases. The pigment tended to collect around the nuclei and in some the entire muscle cell was replaced by pigment granules. Hemofuscin was described in the blood vessel wall in one case. In published accounts[1] mention has been made of a characteristic deposition of hemosiderin in the muscle fibers with fine granules in a spindle-shaped formation at both poles of the nucleus, spreading thence longitudinally through the muscle cell. This pigment consists of both hemosiderin and hemofuscin.

Adrenals. In ten of the thirteen patients in whom a description of the microscopic examination of the adrenals is available, pigmentation was found in the cortex. A remarkable affinity for the zona glomerulosa was noted in seven cases. In one case pigment was found only in the capsule and in two no abnormal pigment was seen. It is noteworthy that in the two cases without pigmentation the diagnosis was made in one at autopsy on the basis of mild hemo-

chromatosis of the liver; the other patient died with carcinoma of the liver. The medulla was not described as pigmented in any case.

Pituitary. Examination of the pituitary was made in five cases but in none was the microscopic picture described. Grossly it was stated to appear normal in two cases. Others have found that the gland may show brown pigmentation grossly and invariably shows hemosiderin deposits chiefly in the gland cells of the anterior lobe.[1]

Thyroid. In four of seven cases in which a description of the microscopic examination of the thyroid is available deposits of iron pigment were noted especially in the alveolar epithelial cells. Sheldon describes the thyroid in hemochromatosis as smaller than normal and unduly hard with a striking deep brown color. He states that microscopically hemosiderin was found in 90 per cent of cases. He also noted a marked overgrowth of connective tissue.

Testes. Specific pigment granules were found in only one of eight patients whose testes were described microscopically. In three cases the testes were atrophied with some fibrosis microscopically in two and marked atrophy of the tubules in the other. Other workers have described atrophy of the germinal epithelium but have stressed that abnormal pigmentation was not marked. Whereas in other organs hemofuscin is usually the only pigment present in blood vessel walls, in the testes in about 20 per cent of cases hemosiderin deposits are confined to these structures.[1]

Prostate. In only one of seven prostates described microscopically was specific pigmentation found; in this case it was detected in the glandular epithelium. Grossly the gland was smaller than normal in three cases and slightly and diffusely enlarged in two others. In Sheldon's cases collected from the literature hemosiderin was described in ten of twenty patients and occurred most frequently in the gland epithelium. Hemofuscin was detected in the musculature of vessels and in the true smooth muscle of the prostate.

Kidneys. In all fifteen cases the kidneys were of normal size and essentially normal in appearance except for a congenital double pelvis with finely granular cortex in one case and a metastatic tumor nodule (from primary carcinoma of the liver) in another. Microscopically, hemosiderin was demonstrated in six of fifteen cases in the renal tubules. The kidneys were remarkable in the paucity of abnormal pigmentation and lack of abnormal findings.

Lungs. Grossly the lungs appeared normal unless the disease was complicated by pneumonia, latent tuberculosis or metastatic tumor. Microscopically, iron-containing brown pigment was found in the alveolar walls or in macrophages in six of twelve cases.

Peritoneal Cavity. Of the fifteen cases seven showed ascites with the presence of 1,000 to 4,500 cc. of fluid.

PATIENTS WITH PROBABLE HEMOCHROMATOSIS

In addition to the thirty proven cases of hemochromatosis already described seventeen patients have been studied whose hepatomegaly, diabetes and skin pigmentation have been highly suggestive of hemochromatosis but in whom a definite diagnosis has not been possible. Of these, seven are dead and ten are living; autopsies were not done in the seven fatal cases.

In this group twelve have had negative skin biopsies for hemochromatosis. However, it is known that deposits of hemosiderin may not be present in the skin in one location and yet be found at a different site or elsewhere in the body especially in the early stages of the disease. Hence a single negative skin biopsy does not conclusively exclude hemochromatosis.

Fourteen of the seventeen patients are males. The average duration of diabetes is 9.7 years in the eight living cases and 3.9 years in the nine fatal cases.

In the seventeen patients the following symptoms and signs were present: skin pigmentation seventeen, diabetes seventeen, hepatomegaly seventeen, weakness sixteen, loss of weight sixteen, splenomegaly thirteen, abdominal pain six and ascites six.

A history of diabetes heredity was obtained in only three patients. The largest average daily insulin dose was 45 units. Alcohol was consumed in moderate or excessive quantities by eight, only occasionally or rarely by two and seven were total abstainers.

In seven patients loss of body hair was evident and in six the testes were found to be atrophied and soft. In three the prostate was markedly atrophied. Unfortunately, our data regarding gonadal hypoplasia are not complete. In six male patients the 17-ketosteroid excretion in the urine was determined and the following values obtained: 8.0, 5.8, 3.3, 1.8, 1.5 and 0 mg. per twenty-four hours (normal range for adult

males 12.3 to 18.5 mg./day). Five patients received testosterone therapy and in three definite improvement in strength and sense of well-being was obtained.

Bromsulfalein determinations of liver function were carried out in six patients and abnormal retention of the dye was demonstrated in two.

The causes of death in the seven fatal cases were stated to be uremia, heart failure, cerebrovascular accident, gastric hemorrhage presumably from ruptured esophageal varices, hemochromatosis, mesenteric embolus secondary to auricular fibrillation and fractured hip. No autopsy was obtained in any of these cases.

TREATMENT

With the introduction of insulin in 1922 and with the development in recent years of more satisfactory methods of the treatment of cirrhosis of the liver, the outlook for the patient with hemochromatosis has improved correspondingly. Furthermore, present day availability of chemotherapeutic agents and antibiotics enable the patient to withstand more successfully intercurrent infections which formerly took a high toll.

The diet should be high in protein (100 to 150 gm. a day) and relatively liberal in carbohydrate (200 to 250 gm. a day). Unless contraindicated because of individual intolerance, fat may be given in amounts required to maintain satisfactory body weight (usually 60 to 100 gm. a day). Edema and ascites may make the restriction of sodium desirable. The diet should be supplemented with large amounts of vitamin B complex. In certain patients the use of crude liver extract intramuscularly may be tried,

It is important that the diet be carefully planned and followed and that the diabetic condition be kept under excellent control. Insulin in dosage to maintain satisfactory blood sugar levels should be prescribed. In our patients protamine zinc insulin alone or together with unmodified insulin has been used in recent years as with other diabetic patients.

If ascites appears it should be treated with the usual measures. If success does not follow the use of a minimal sodium diet and mercurial diuretics, recourse to paracentesis may be necessary.

Because of the huge excess of iron already in the body treatment with iron should be avoided even though anemia may be present.

In our series nine patients, four in the proven and five in the probable group, received testosterone because of evidence of gonadal hypoplasia. In at least five of these there was a gratifying improvement in strength and well-being which at times was quite striking. The dosage used was 25 mg. two or three times a week intramuscularly. If beneficial, this was followed up by the implantation of pellets of testosterone subcutaneously.

Finch and associates[11] have investigated the possibility of treating hemochromatosis by depleting body stores of iron with repeated venesections. Some success has been achieved in a small group of patients by removal of blood at weekly intervals over months and even years of time. One cannot help but wonder whether the infrequency of hemochromatosis in women may be related to the periodic loss of menstrual blood.

COMMENTS

The studies reported in this article have yielded information of interest clinically. They have shown the usual course of patients with hemochromatosis and have demonstrated the greater length of life which is possible with present day treatment of both major aspects of the condition —diabetes and cirrhosis of the liver. They have not, however, aided greatly in the understanding of the basic cause of bronze diabetes. The pathogenesis of the disordered iron metabolism remains in large part obscure.

Throughout the years various theories have been proposed to explain the excessive accumulation of iron-containing pigment in the body. Such accumulation may take place in almost every organ and tissue. Its magnitude is shown by the fact that whereas the liver normally contains only about 1 to 2 gm. of iron, in cases of hemochromatosis this may amount to as much as 50 gm. or more.[1]

In 1920 Mallory and co-workers[12] proposed the theory that hemochromatosis might be due to chronic copper poisoning acquired by drinking alcohol or eating food prepared in copper vessels. In rabbits they were able to produce a pigment cirrhosis by the prolonged feeding of copper salts. The pigment granules were regarded as those of hemofuscin which they suggested might then give rise to hemosiderin. However, subsequent work has failed to support Mallory's theory as it pertains to man and at present it is generally held unlikely that copper poisoning plays any significant role in the hemochromatosis of human subjects.

A more satisfying explanation for the pathogenesis of hemochromatosis is the view that it

represents an inborn error of metabolism in which an abnormal accumulation of iron in the body occurs probably due to increased absorption. It has been assumed that the retention of iron has occurred at a slow rate over many years of time since, at best, iron balance studies in patients with hemochromatosis have shown only slightly positive balances.[3,13,14]

The validity of iron balance studies in the past seemed open to question when the report by Mitchell and Hamilton[15] appeared. These workers suggested that in normal subjects an appreciable loss of iron occurs regularly in the sweat. In fact, the amount lost in the sweat in a person under comfortable conditions of heat and humidity was found in their studies to be six times that excreted in the urine. Under hot, humid conditions the amount lost in the sweat was over fifty times that in the urine (37 per cent of an ingested dose in sweat as compared with 0.7 per cent in urine). This work of Mitchell and Hamilton attracted attention particularly because it had been assumed previously[16] that for practical purposes the body possessed no means for the excretion of iron. Studies had shown that iron is excreted by the kidneys and bowel in amounts very small as compared with intake. It had been proposed, therefore, that normally the body absorbs iron only according to need and uses this amount over and over. The findings of Mitchell and Hamilton would necessitate revision of this view. However, still more recently Adams, Leslie and Levin[17] studied the iron content of sweat in twenty-five normal persons with especial attention to cellular as opposed to non-cellular components. After centrifugation they found the clear supernatant fluid to be essentially free of iron whereas the opalescent, uncentrifuged sweat had a high iron content. These findings suggested that the dermal loss of iron, albeit considerable, is not a function of sweating but of desquamation of skin.

SUMMARY

1. Thirty cases of proven and seventeen cases of probable hemochromatosis with diabetes are presented together with postmortem findings in fifteen of the proven cases. In the proven cases the diagnosis was verified by skin biopsy, liver biopsy or autopsy.

2. Of the thirty proven cases three were females. The age at onset of diabetes varied from 36.7 to 78.1 years. Because the onset of symptoms was so indefinite the date of onset of hemochromatosis could not be established.

3. Of the thirty patients three are living, with duration of diabetes of 13.0, 8.8 and 5.7 years, respectively. Among the fatal cases the average age at death was 57.8 years and the duration of diabetes 4.9 years.

4. The average insulin requirement was somewhat greater than that of most diabetic patients and one patient died in coma while receiving 1,600 units daily. However, insensitivity to insulin was not invariable; seventeen of the thirty cases never took more than 50 units of insulin daily.

5. With present day treatment of both diabetes and cirrhosis of the liver a longer life is possible for the patient with hemochromatosis. However, paucity of knowledge regarding the basic defect makes specific therapy impossible as yet. Possible new approaches to this problem are discussed.

REFERENCES

1. Sheldon, J. H. Hemochromatosis. London, 1935. Oxford University Press.
2. Root, H. F. Insulin resistance and bronze diabetes. *New England J. Med.*, 201: 201–206, 1929.
3. Marble, A. and Smith, R. M. Studies of iron metabolism in a case of hemochromatosis. *J. Lab. & Clin. Med.*, 12: 1592–1603, 1939.
4. Fishback, H. R. Clinical demonstration of iron in skin in hemochromatosis. *J. Lab. & Clin. Med.*, 25: 98–99, 1939.
5. Rath, C. E. and Finch, C. A. Chemical, clinical and immunological studies on the products of human plasma fractionation. Serum iron transport. Measurement of iron-binding capacity of serum in man. *J. Clin. Investigation*, 28: 79–85, 1949.
6. Rous, P. Urinary siderosis: haemosiderin granules in the urine as an aid in the diagnosis of pernicious anemia, hemochromatosis and other diseases causing siderosis of the kidney. *J. Exper. Med.*, 28: 645–658, 1918.
7. Jeanselme, M. E. De l'impermeabilité aux rayons Roentgen des organes contenant du pigment ocre. *Presse méd.*, 5: 59, 1897.
8. Gowdy, J. F., Riemanschneider, P. A., Dealy, J. B. and Sosman, M. C. Roentgenological findings in hemochromatosis. *Am. J. Roentgenol.* In press.
9. Desforges, G. Abdominal pain in hemochromatosis. *New England J. Med.*, 241: 485–487, 1949.
10. Drake, W. L., Jr. Personal communication.
11. Finch, S., Haskins, D. and Finch, C. A. Iron metabolism. Hematopoiesis following phlebotomy. Iron as a limiting factor. *J. Clin. Investigation*, 29: 1078–1086, 1950.
12. Mallory, F. B., Parker, F., Jr. and Nye, R. N. Experimental pigment cirrhosis due to copper and its relation to haemochromatosis. *J. Med. Research*, 42: 461–490, 1920.

13. Dry, T. J. Hemochromatosis: its relation to the metabolism of iron and copper. *Minnesota Med.*, 17: 301–312, 1934.
14. Fowler, W. M. and Barer, A. P. Iron metabolism in hemochromatosis. *J. Lab. & Clin. Med.*, 23: 47–52, 1937.
15. Mitchell, H. H. and Hamilton, T. S. The dermal excretion under controlled environmental conditions of nitrogen and minerals in human subjects with particular reference to calcium and iron. *J. Biol. Chem.*, 178: 345–361, 1949.
16. Johnston, F. A. The new theory of iron metabolism. *J. Am. Dietet. A.*, 19: 838–840, 1943.
17. Adams, W. S., Leslie, A. and Levin, M. H. The dermal loss of iron. *Proc. Soc. Exper. Biol. & Med.*, 74: 46–48, 1950.

Seminars on Arteriosclerosis

Hypercholesteremia with Predisposition to Atherosclerosis*

An Inborn Error of Lipid Metabolism

DAVID ADLERSBERG, M.D.
New York, New York

GARROD,[1] in the first decade of the present century, was able to classify only four disorders of metabolism as "inborn": albinism, alcaptonuria, cystinuria and pentosuria. He characterized these conditions as "metabolic sports, the chemical analogues of structural malformations." Since then many additional inborn errors have been recognized, involving every branch of metabolism and representing important and not altogether innocuous clinical entities.[2] These include periodic paralysis, hemochromatosis and primary amyloidosis; such inborn faults of protein metabolism as cystinuria, alcaptonuria, phenylpyruvic oligophrenia, histidinuria and tyrosinosis; and inborn errors of carbohydrate metabolism, such as renal and pseudorenal glycosuria, pentosuria, fructosuria, galactosuria, maltosuria, sucrosuria and lactosuria, as well as glycogenosis (von Gierke's disease). Many more inborn errors of metabolism doubtless remain to be recognized.

INBORN ERRORS OF LIPID METABOLISM

In the field of disorders of lipid metabolism (the lipidoses) certain inborn errors have long been recognized. Storage of sphingomyelin in the reticulum cells and histiocytes of the organs is the characteristic feature of Niemann-Pick's disease (*sphingomyelin lipidosis*). In this disease hepatosplenomegaly, retardation of growth, mental deterioration and cachexia are the outstanding features. Fatal termination in early childhood is the rule;[3] only in rare instances is longer life compatible with the disease.[4] The combination with familial amaurotic idiocy (Tay-Sachs' disease) is considered a variant of Niemann-Pick's disease.[5]

Sphingomyelin lipidosis is characterized by familial occurrence.[6–9] Malformations observed in some cases, such as microgyria and polydactylia are additional evidences of the degenerative hereditary character of this disorder.[10] A simple recessive as well as an irregularly dominant mode of transmission, with a prevalence in males, have been suggested;[4,10] the latter seems to be more likely. There is a striking predisposition among Jews to sphingomyelin lipidosis, the proportion of non-Jewish to Jewish infants being 1:3.[10]

In Gaucher's disease an abnormal type of cerebroside (kerasin), containing glucose instead of galactose, accumulates in the organs, especially in the spleen.† *Cerebroside lipidosis* is, except for an infrequently occurring infantile form, a protracted chronic disease[12] with clinical features of hepatosplenomegaly, anemia, neutropenia and thrombocytopenia.

There are extensive studies concerning the familial occurrence of cerebroside lipidosis.[13–19] While horizontal spread is frequently encountered, vertical spread is rarely evident. The disease has the tendency to increase in severity with every transmission; it affects members of succeeding generations at ever earlier ages and thus eventually extinguishes itself.[16] It must be stressed that in the study of

† A discussion of the chemical, physiologic and pathologic aspects of blood and tissue lipids and lipoproteins was presented in a preceding article of this series.[11]

* From the Medical Services of The Mount Sinai Hospital, New York, N. Y. Original work of the author and his co-workers discussed in this paper was in part supported by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

affected families, subclinical forms of the disease can be detected (in asymptomatic carriers) by sternal bone marrow studies only, a principle which unfortunately was not observed in older studies. On the basis of recent observations[10,16–18] cerebroside lipidosis begins as a genetic mutation which, once established, is transmitted as a simple dominant trait.[16] "Its frequency amongst the Jews has been mentioned in all the publications."[10]

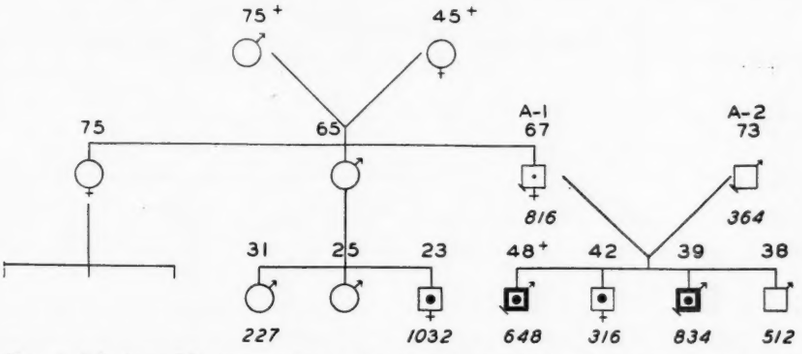


FIG. 1. Mating of heterozygotes, A-1 and A-2, producing four persons with elevated serum cholesterol, three with xanthoma and two with coronary artery disease. The numbers above the symbols indicate age of the person; those below the symbols indicate serum cholesterol in mg. per 100 ml. For explanation of symbols, see Figure 2. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

In primary xanthomatosis, cholesterol is deposited in large quantities in various tissues of the body (*cholesterol lipidosis*). Cholesterol lipidosis[20] is usually a prolonged and chronic disease essentially benign in nature. The clinical manifestations include xanthelasma or xanthoma planum, xanthoma tuberosum of the skin, xanthoma tendinosum, and infiltration of the endocardium and arterial intima by large pale foam cells loaded with cholesterol.* Primary cholesterol lipidosis (xanthomatosis) must be distinguished from secondary cholesterol lipidosis which may be observed in certain pathologic conditions, such as prolonged biliary obstruction or uncontrolled diabetes.

HEREDITARY ASPECTS OF PRIMARY CHOLESTEROL LIPIDOSIS (XANTHOMATOSIS)

The genetic mechanisms of primary cholesterol lipidosis have been extensively studied.[10,22–31] Opinions as to the mode of transmission vary considerably. Investigators who used the presence of cutaneous lesions as a criterion of the trait obtained different results from those who selected the abnormal cholesterol level as the identifying characteristic. At one extreme of opinion the disease is considered to be transmitted as a recessive trait.[27] This mode of transmission is unlikely if the frequency of the gene for this condition in the general population should prove to be low (less than 0.5 per cent) because in that case a significant increase in the incidence of cousin marriages among the parents of affected persons should be observed and this has not been noted.[32] An attempt was made[31] to determine whether increased serum cholesterol levels, or xanthoma, or both, were dominant traits by studying a family of ten siblings, several of whom exhibited the full syndrome (hypercholesteremia, xanthoma and cardiovascular disease). The results of this study, as well as previous observations[25] and our later studies[32] support the concept that this syndrome is inherited as a dominant trait and that hypercholesteremia rather than xanthomatosis is the principal manifestation of the inherited factor. The best evidence to date that familial hypercholesteremia is transmitted as an (incomplete) dominant trait was presented recently.[33]

Our studies confirmed the postulate that hypercholesteremia represents the heterozygous abnormal state while xanthoma represents the homozygous abnormal state.[28,32] Descent tables of thirty-five xanthoma families were presented to clarify these factors. Figure 1 illustrates the transmission of the metabolic fault as a dominant trait. In this kindred both parents (A-1 and A-2) had elevated cholesterol levels. All four of their offspring had hypercholesteremia, three

* Addison and Gull,[21a] exactly 100 years ago, described xanthomas as vitiligoidea plana and tuberosa. The character of the large pale xanthoma cells (foam cells) remained obscure for over fifty years until Pick and Pinkus[21b] recognized the cell content as lipid deposits and interpreted them as a manifestation of a metabolic disturbance.

had xanthoma and two had coronary artery disease; both parents as well as two of the offspring had corneal arcus. It was assumed that the mating of heterozygotes A-1 and A-2 (each of whom carried one gene responsible for abnormal cholesterol metabolism) produced homozygous abnormal persons with severe disease, i.e., xanthoma. These xanthomatous subjects in all probability carry two genes responsible for abnormal cholesterol metabolism. Our data revealed that, with one exception, patients with xanthoma were the offspring of two hypercholesteremic parents and that every patient in the entire series who exhibited xanthoma, i.e. who was an abnormal homozygote, had hypercholesteremia.

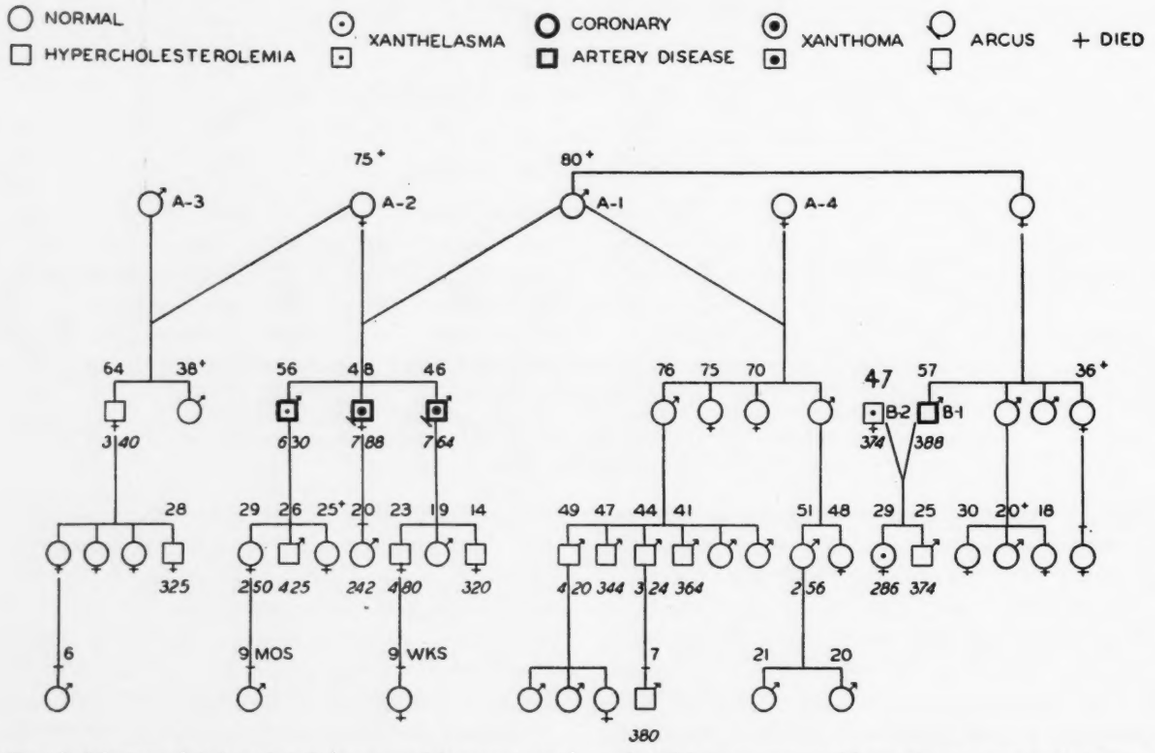


FIG. 2. Mating of A-1 and A-2 (presumed heterozygotes) produced homozygotes with xanthoma, coronary artery disease and greatly elevated serum cholesterol. Mating of A-3 with A-2 (presumed normal with presumed heterozygote) produced hypercholesteremic offspring as did union of A-4 with A-1 (presumed normal with presumed heterozygote). Mating of known hypercholesteremic subjects B-1 and B-2, produced one offspring with serum cholesterol of 374 mg. and another with serum cholesterol of 286 mg. per 100 ml., and xanthelasma. The symbols at top of this figure apply also to Figures 1 and 3–5. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

A kindred in which hypercholesteremia was traceable through three generations is presented in Figure 2. In the mating of A-1 and A-2 there were three offspring, all of whom had hypercholesteremia and coronary artery disease; in addition, two of them had xanthoma tendinosum. In five of the seven grandchildren, serum cholesterol determinations were performed and revealed hypercholesteremia in three. Both A-1 and A-2 had been married previously and each had had offspring from the previous partner. Two of the seven living descendants resulting from the earlier union of A-2 and A-3 were studied; both persons exhibited hypercholesteremia without manifest disease. Finally, the union of A-1 and A-4 had resulted in four offspring, one of whom had ten descendants. Of these ten persons five were examined; they had elevated serum cholesterol but no evidence of heart disease or xanthoma. Examination of a son of a sibling of A-1 revealed hypercholesteremia and coronary artery disease (B-1). His wife, B-2, was not a member of the original family but had xanthelasmas and hypercholesteremia. The mating of B-1 and B-2 resulted in two offspring, whose serum cholesterol levels were 374 and 286 mg. per 100 ml. Genetic analysis of this family tree indicates then that A-1 and A-2 presumably had hypercholesteremia; their union resulted in a high incidence of hypercholester-

emia, xanthoma and heart disease. The previous union of A-2 with A-3 (presumably normal) reduced considerably the incidence of manifest lesions in the offspring. Similarly, the previous union of A-1 and A-4 (presumably normal) resulted in a lower incidence of manifest signs.

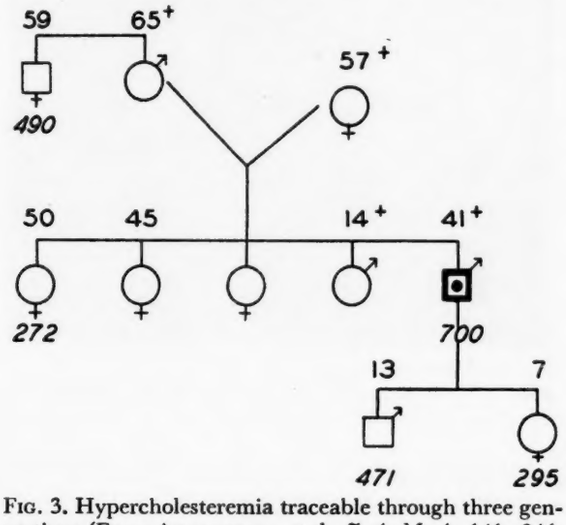


FIG. 3. Hypercholesteremia traceable through three generations. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

However, hypercholesteremia alone was exhibited by descendants in the third generation. Figure 3 shows another family in which hypercholesteremia could be traced through three generations.

Figure 4 presents six siblings of whom four had coronary artery disease; in three of the four persons sudden death occurred due to acute myocardial infarction. The index patient, B-3, was admitted to the hospital with coronary thrombosis at the age of forty-three. This woman presented xanthelasmas and a serum cholesterol level of 525 mg. per 100 ml.; she died suddenly a few months later. Investigation of the surviving family members revealed xanthoma in one, coronary artery disease in another, but hypercholesteremia in all. B-5 and B-6 were known to have died of myocardial infarction at the ages of thirty-seven and thirty-one, respectively. The autopsy record of B-6 revealed far advanced atherosclerosis in a young man. The true nature of this patient's disorder became apparent fourteen years after his death when a study of the entire family was undertaken. Two daughters of the index patient, whose ages were sixteen and twenty-four years, exhibited serum cholesterol levels of 535 and 540 mg. per 100 ml., respectively.

Figures 5 and 6 illustrate the skin and tendon lesions observed in members of xanthoma families.

The entire series consisted of 172 members of thirty-five families and of twenty-nine patients with xanthomatosis whose families were not

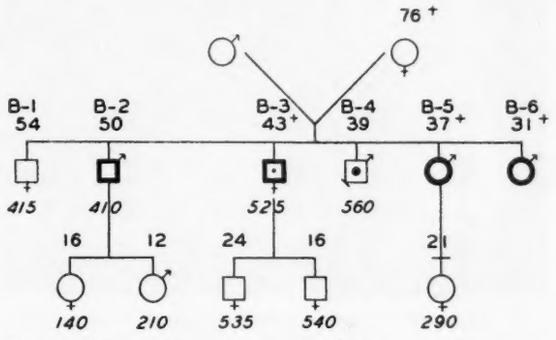


FIG. 4. Four of six siblings exhibiting coronary artery disease, with death of three of them at forty-three, thirty-seven and thirty-one years of age, respectively. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

available for study, a total of 201 persons. The most frequently encountered abnormality was hypercholesteremia (60 per cent) and next in frequency was coronary atherosclerosis (40 per cent). Xanthelasma and corneal arcus followed in frequency (30 and 18 per cent, respectively); tuberous or tendinous xanthoma was the least frequent stigma (12.5 per cent). Thus the sign from which the disorder derives its name was surpassed in frequency by the other stigmata of the disease, especially hypercholesteremia and coronary artery disease.

There are no statistical data available concerning the occurrence of primary cholesterol lipidosis (xanthomatosis) among various peoples. The disorder has been described chiefly in white persons. Thannhauser[10] noted that "although no statistics are available, the incidence of cases seems larger in the Semitic then in other races." Thus primary cholesterol lipidosis seems to share two features with sphingomyelin lipidosis and cerebroside lipidosis: dominant genetic transmission and more frequent occurrence in Jews.

INVOLVEMENT OF CARDIOVASCULAR SYSTEM IN PRIMARY CHOLESTEROL LIPIDOSIS (XANTHOMATOSIS)

Involvement of the cardiovascular system in xanthomatosis was observed as early as 1873.[20b] Coronary artery disease or occlusive vascular disease of the extremities was noted in 40 per

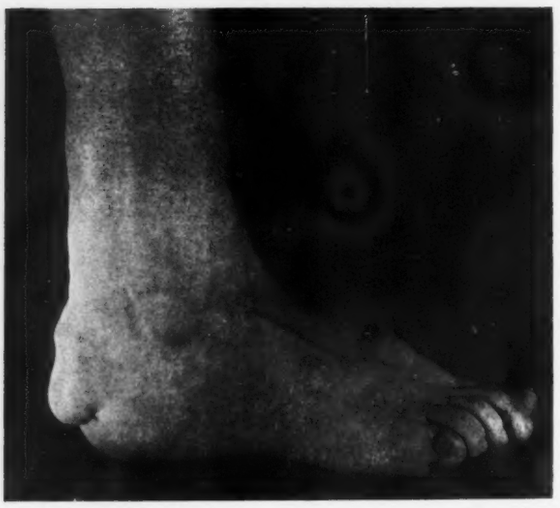


FIG. 5. Achilles tendon xanthoma in a member of a xanthomatous family. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

FIG. 6. Xanthoma tendinosum of hand of a member of family presented in Figure 3. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

cent of a group of sixty-five patients with xanthoma studied at the Mayo Clinic.[34] The occurrence of sudden death from cardiovascular accidents in young persons with xanthoma has been frequently emphasized.[10,31,35] In our own material[32] of thirty-five tainted families composed of 172 persons, fifty-four members exhibited coronary artery disease; serum cholesterol was examined in forty of the fifty-four persons and was elevated in thirty-eight.

One might suspect that the frequent association of xanthoma and coronary artery disease in members of these families could be due to the possibility that atherosclerosis, like xanthoma, represents the homozygous abnormal state. This is not the case because not all patients with coronary artery disease, as is well known, exhibit hypercholesteremia and xanthoma. The abnormal homozygote would, by definition, present hypercholesteremia and, in addition, tendinous or tuberous xanthoma.

UNSELECTED YOUNG PATIENTS WITH CORONARY ARTERY DISEASE

The association of xanthomatosis with coronary atherosclerosis and myocardial infarction is of great clinical importance. It must be stressed in this connection that xanthoma families are by no means rare and that in many members of these families the only manifestation of the disease may be coronary artery disease at an early age and/or a high level of serum cholesterol.[28] Thannhauser and Magendantz used the term "forme fruste of essential hypercholesteremic xanthomatosis" to characterize the monosymptomatic cases without skin xanthoma but with high serum cholesterol.[26] In several families of our observation such individuals have subsequently sustained cardiac infarction. Another feature which may be found in relatively young persons belonging to the xanthoma families is corneal arcus.*[29,36,37]

In the course of our studies we observed young adults with coronary atherosclerosis who were not known members of xanthoma families but who nevertheless presented elevated serum cholesterol levels and corneal arcus.[29] The not infrequent association of these three pathologic states, namely, abnormally high serum cholesterol levels, coronary artery disease and corneal arcus, in the same individual suggested that this association might be more than coincidental. Since pathologic alteration of lipid metabolism is apparently the underlying metabolic disturbance predisposing to coronary artery disease in young members of xanthoma families, it appeared profitable to study the serum cholesterol systematically and to search for those stigmata that frequently occur in association with hypercholesteremia, in a group of younger patients with established coronary atherosclerosis and in their siblings.

* We consider the designation "corneal arcus" preferable to "arcus senilis" or "arcus juvenilis." Since the arcus of the cornea is etiologically not related to age, the term "corneal arcus" is purely descriptive and applies to any age. The longer Latin term "arcus corneae lipoides" is also occasionally used.

The working hypothesis then, was, that familial xanthomatosis may represent only the extreme degree of disturbed lipid metabolism and that many patients with seemingly uncomplicated coronary artery disease might fall into a similar pattern. It was believed that if this hypothesis could be confirmed by clinical observation, it might help to explain the familial occurrence of coronary artery disease and also support the concept that a disturbed lipid metabolism plays a role in the etiology of coronary atherosclerosis.

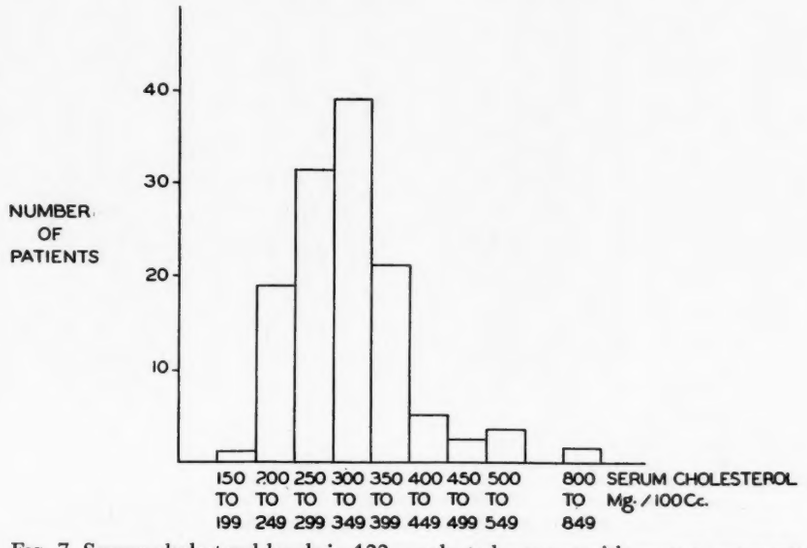


FIG. 7. Serum cholesterol levels in 122 unselected persons with proven coronary artery disease. (From ADLERSBERG et al., *J. A. M. A.*, 141: 246, 1949.)

A group of 122 patients, 108 men and 14 women was studied.[29] Each patient was examined for the presence of arcus, xanthelasma and xanthoma; one or more serum cholesterol determinations were performed by the method of Bloor.* The average age of the group was forty-five years; the average age at the onset of symptoms was forty-two years. Most persons were between thirty-five and fifty years of age, the youngest was twenty-seven and the oldest sixty-four. Patients who were older than fifty years at the time of the study had developed angina pectoris before the age of fifty.

In addition to these index patients an attempt was made to study and evaluate all the available immediate family members. We were able to examine fifty families of the 122 patients, and collected data on all or most of their siblings. In each of three families of six to seven siblings only three members were available for study. In the history of the siblings pertinent data were recorded, such as heart disease, diabetes and hypertension. The presence or absence of corneal arcus, xanthelasma and xanthoma was noted and the serum cholesterol was determined.

In all, 307 serum cholesterol analyses were made. The serum cholesterol level among the primary patients ranged from 199 mg. to 845 mg. per 100 ml.; the mean was 316 mg. per 100 ml. (± 7.49 S.D.$_m$). Of the 122 patients, seventy-one (58 per cent) had a serum cholesterol level above 300 mg. per 100 ml. (Fig. 7.) The average serum cholesterol of these seventy-one persons was 365 mg. per 100 ml. Patients known to be members of xathomatous families were excluded from this study. Nevertheless, twenty-two patients of the group exhibited corneal arcus, twelve had xanthelasma and three had skin or tendon xanthoma. Among the twenty-two patients with corneal arcus and coronary artery disease seventeen had hypercholesteremia; among the twelve patients with xanthelasma and coronary artery disease nine had hypercholesteremia; and among the three with skin or tendon xanthoma and coronary atherosclerosis all had hypercholesteremia.

Of the fifty families studied, many exhibited hypercholesteremia. There were fifteen families (30 per cent) in which all or most of the siblings

* In our studies a serum cholesterol level of at least 300 mg. per 100 ml., by the Bloor method, and 280 mg. per 100 ml., by the Sperry-Schoenheimer method, was selected as indicative of hypercholesteremia. The influence of minor fluctuations and elevations of serum cholesterol is thus eliminated.[32,74b]

TABLE 1*

SERUM CHOLESTEROL LEVELS AMONG SIBLINGS OF PATIENTS WITH CORONARY ATHEROSCLEROSIS

(*From Boas et al., Am. Heart J.*, 35: 611, 1948)

No.	Patient	Serum Cholesterol (mg./100 ml.)	Serum Cholesterol of Siblings (mg./100 ml.)						Remarks
			Sibling 1	Sibling 2	Sibling 3	Sibling 4	Sibling 5	Sibling 6	
1	F. Z.	345	330	320	304	240			Sibling 5, woman, died age 46 of "heart attack"; mother died age 76 "heart attack"
9	L. K.	318	318	310	287				Sibling 3, woman 50 yr. of age, hypertension
4	C. W.	285	339	322	319	?†			Sibling 2, man, hypertension
8	M. K.	327	318	320	263	?	?		Sibling 1, man, cardiac infarction, age 32
2	S. K.	335	350	212					Sibling 1, man 51 yr. of age, hypertension; mother died age 72, hemiplegia
3	I. F.	500	435	308					
14	S. D. R.	374	303	235					
5	C. J.	315	325	330	?				
7	L. P.	300	328	241	?				Sibling 2, man, hypertension and auricular fibrillation
13	M. T. S.	336	424	308	?	?	?		
10	H. B. P.	322	350	325	?	?	?	?	Sibling 3, woman, died age 38, "stroke"; sibling 4, woman, died age 52, "stroke"; sibling 5, woman, age 66, died "heart disease"; mother died age 58, diabetes and "heart trouble"
11	I. S.	362	362						
15	J. N.	358	408						
6	H. R.	390	370	?					Mother died age 52, diabetes mellitus; father died age 62, "heart attack"
12	B. S.‡	518	?						Four children; cholesterol values of 368, 326, 311 and 246
24	A. R.	330	296	?					Sibling 2, man, died cardiac infarction, age 41; mother and father died of "heart disease"
27	A. C. K.	282	325						Father, age 70, has coronary artery disease
44	J. B. B.	230	300						
45	P. M.	277	366						Sibling, woman 59 yr. of age, has hypertension and coronary artery disease
46	C. R.	340	330	280	274				
47	M. S. L.	342	240						
48	A. S.	314	232						Father died age 58, cardiac infarction
49	J. W.	265	343						
50	J. B.	330	268						Father died age 57, cardiac infarction

40	E. R.	357	350	292	283	260	246	?	Sibling 1, man 50 yr. of age, has coronary sclerosis
25	P. K.	263	270	248	261	?	?	?	
18	I. T. K.	220	325	284	257	232	220		
21	J. W. W.	425	306	274	257	168	140		
28	H. A.	272, 238	357	262	241	220	220		Sibling 1, man aged 38, has arcus senilis
31	I. R.	311	196	178	168	?	?		Father, aged 60, died coronary artery disease
34	I. G.	199	256	246	224	?	?		Sibling 1, woman aged 48, hypertension and angina pectoris; sibling 2, man aged 46, hypertension; sibling 3, man aged 54, angina pectoris
23	A. B.	351	300	286	?	?	?		
37	B. R.	336	357	241	227	207			Sibling 1, man aged 40 yr., has marked arcus; father died 58, cardiac infarction; mother has angina pectoris
16	H. N.	284, 256	278	263	187	?			
20	J. P.	350	277	210	206	?			
41	S. D.	333, 355	245	214	198	?			All siblings have hypertension
29	S. K. B.	236	270	217	?	?			
17	M. R. S.	332	293	260	255				
22	A. H.	289	320	276	246				
30	O. S.	232	278	263	184				
43	J. H.	224	238	212	165				
26	H. K. M.	260	270	244	?				
32	J. L.	215	182	167					Mother, aged 53, hypertension and angina pectoris
33	G. S. S.	360	292	26					Father died age 46, arteriosclerosis; sibling 1, woman, hypertension and arteriosclerosis
36	I. K.	225	216	208					Sibling 2, man, died cardiac infarction at 58; both parents died of hypertensive arteriosclerotic heart disease
39	B. G.	330, 330	241	202					Mother has coronary artery disease, father has hypertension
19	N. M.	220	200						Sibling, man, cardiac infarction, age 40
35	H. S. B.	287	297						Sibling, man, had cardiac infarction, age 49
38	S. P. P.	254	207						
42	M. C.	269	264						Father, age 67, has coronary sclerosis and cholesterol of 232

* The first 15 families listed are those in which hypercholesteremia was present in all or most siblings. The next 9 families listed are those in which one-half the members exhibited hypercholesteremia and one-half had normal serum cholesterol. The remaining 26 families are those in which there was no general tendency to hypercholesteremia although an occasional sibling exhibited hypercholesteremia.

† ? indicates sibling unavailable for study.

‡ Since there were no living siblings, the children were studied.

showed an abnormal serum cholesterol level; they are the first fifteen families presented in Table 1. In nine families one-half of the members exhibited hypercholesteremia, while the other half had normal cholesterol figures; they follow the first fifteen families in Table 1. In the remaining twenty-six families an occasional sibling exhibited hypercholesteremia, but no general tendency toward abnormally high serum cholesterol level was noted. In a few instances the primary patient exhibited normal serum cholesterol but the siblings had hypercholesteremia or the clinical signs of disturbed lipid metabolism.

It was of interest to compare the results obtained in the xanthoma families with those in unselected patients with coronary artery disease and in their families. In xanthomatous families there was a very high incidence of both hypercholesteremia and coronary artery disease and with few exceptions these abnormalities were exhibited at a relatively young age. Hypercholesteremia was also frequently found in unselected patients with coronary disease under the age of fifty and in their siblings. Thus in agreement with our working hypothesis, elevation of the serum cholesterol level seemed to represent the link between what had appeared to be two distinct groups.

The clinical significance of hypercholesteremia in the siblings of patients with coronary artery disease has been proven by Stecher and Hersh.[38] These authors applied a standard genetic test to thirty-seven of the fifty families of hypercholesteremia investigated by us. The thirty-seven families included 126 children, of whom sixty-seven exhibited elevated serum cholesterol levels. The proportion of children expected to be affected if one parent were hypercholesteremic and the other normal would be 50 per cent of the total. Because the number actually affected with hypercholesteremia closely fits this 1:1 Mendelian ratio, it is probable that in these families as well as in the xanthoma families a hereditary mechanism is involved. By analogy with similar data obtained in other hereditary diseases it is probable that the metabolic disturbance of hypercholesteremia is transmitted as a dominant trait.

The common factor among most patients of young age with coronary atherosclerosis appears to be a hereditary disorder of lipid metabolism manifested by hypercholesteremia. The observation of the disease in several members of one family and its manifestation in young persons may be explained on this basis. We are inclined to consider familial xanthomatosis as the severe form of the inherited disturbance while the patients exhibiting only coronary artery disease in the unselected group would represent the milder form of the same disturbance. Of course, the observation of hypercholesteremia *per se* does not indicate whether the patient belongs to a family with the severe or mild form of cholesterol lipidosis.

INCIDENCE OF HEREDITARY HYPERCHOLESTEREMIA

The reported studies dealt only with single families or with families or individuals known to have either xanthomatosis or coronary artery disease. An attempt was then made to estimate the incidence of the inborn error of lipid metabolism as manifested by hypercholesteremia in a larger and less selected population.

In the first study 200 individuals (index patients) representing 200 consecutive unselected admissions to a male and female ward of Mount Sinai Hospital were surveyed.[39] On admission a careful personal and family history was obtained from the patients and the physical examination took special consideration of the signs and symptoms usually associated with a disturbed lipid metabolism, such as xanthoma, xanthelasma, corneal arcus and coronary artery disease. Next morning a specimen of venous blood was drawn after a fast of at least twelve hours for the determination of serum cholesterol. Whenever the history, physical examination or serum cholesterol level suggested the possibility of hereditary hypercholesteremia, serum cholesterol determinations were performed on all available members of the immediate family. The Sperry-Schoenheimer method has been exclusively used for this study.

Of the 200 index patients, a total of forty-seven were found to have serum cholesterol levels exceeding 280 mg. per 100 ml. The serum cholesterol of these patients varied from 282 to 655 mg., average 338 mg. per 100 ml. A group of fifteen of these forty-seven patients were suffering from diseases which are associated with hypercholesteremia: biliary obstruction with icterus, nephrosis, myxedema and uncontrolled diabetes. A second group of patients included nine with elevated serum cholesterol levels not caused by their primary disease. In all of these patients the possibility of hereditary hypercholesteremia arose, but in each case

further examination of the family was impossible, usually because all the family members lived in widely separated areas. In a third group of twelve patients with "idiopathic" hypercholesteremia family members were studied without adequate evidence for the presence of a hereditary background. Often only one or two members of a family presented hypercholesteremia while the others were normocholesteremic or were not available for study. Finally, twelve patients had serum cholesterol levels in excess of 280 mg. per 100 ml., exhibited no disease of the type observed in the first group and usually associated with hypercholesteremia, and had at least two close relatives with hypercholesteremia. The proven incidence of hereditary hypercholesteremia in this series of 200 families was, then, 6 per cent. A typical family is presented in Figure 8.

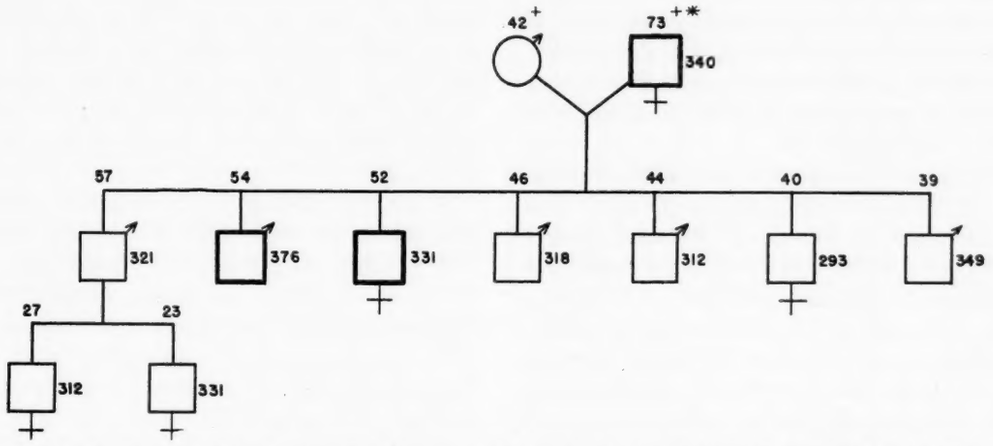


FIG. 8. Family tree of A. S., seventy-three year old woman, index patient (as indicated by *). She was admitted to the hospital with acute myocardial infarction and died twenty-four hours later. Her husband died suddenly at the age of forty-two. Seven of her children had hypercholesteremia, two coronary heart disease. Two grandchildren, ages twenty-seven and twenty-three, also had elevated serum cholesterol levels.

In establishing a criterion for the presence of hereditary hypercholesteremia, various considerations had to be taken into account. The chief factor was the "random incidence" of hypercholesteremia, which is unknown. Of the 200 index patients forty-seven were hypercholesteremic. Deducting fifteen patients whose diseases are commonly associated with hypercholesteremia, thirty-two of 185 patients or 17.3 per cent was computed to be the random incidence of idiopathic hypercholesteremia. By selecting the criterion of three members in a family the possibility of hypercholesteremia being present by chance would be only 0.5 per cent (17.3% × 17.3% × 17.3%). A chance incidence of 0.5 per cent was infrequent enough to justify basing the criterion of hereditary hypercholesteremia on the presence of hypercholesteremia in at least three immediate members in a family. In the first series, then, the observed incidence of 6 per cent had to be reduced to allow for random occurrence by 0.5 per cent and thus the revised incidence of hereditary hypercholesteremia was 5.5 per cent. This incidence probably represents a minimum since some cases of hereditary hypercholesteremia probably remained undetected.

In a second series 300 more consecutive admissions to the hospital were surveyed for the presence of hereditary hypercholesteremia.[40] The random incidence of "idiopathic" hypercholesteremia in these cases was 13.7 per cent. The chance incidence of idiopathic hypercholesteremia in two immediate family members was 13.7 per cent × 13.7 per cent or 1.9 per cent, while the possibility of hypercholesteremia being present by chance in three immediate family members was only 0.26 per cent (13.7% × 1.9%). The chance incidence of 0.26% was again low enough to justify on genetic grounds the presence of hypercholesteremia in at least three members in a family as a criterion of the hereditary nature of the hypercholesteremia. The observed incidence of hereditary hypercholesteremia was found to be 4.11 per cent. When corrected for chance occurrence, the corrected incidence then became 3.85 per cent. The esti-

mated incidence of hereditary hypercholesteremia studied in both groups of 500 families is, then, between 4 and 5 per cent.

The frequency of this disorder of lipoid metabolism is thus much higher then was suspected. In this connection it might briefly be mentioned that a survey performed by Wilkerson and his co-workers to determine the general incidence of diabetes mellitus in a representative town (Oxford, Massachusetts), also revealed a much higher occurrence of this metabolic disorder than suspected.[41]

Detailed analyses of the first 200 families studied revealed several interesting facts.[39] No proven instance of hereditary hypercholesteremia was found in the non-white families studied although they composed 10 per cent of the group. There was a high incidence of this metabolic abnormality among families of Jewish descent. In 104 Jewish families eleven instances of proven hereditary hypercholesteremia (10.6 per cent) were encountered whereas in ninety-six non-Jewish families this abnormality was observed in only one instance (1 per cent). Although these differences may be coincidental because of the limited number of observed families, it should be recalled that other inborn errors of lipid metabolism are also frequently encountered in Jews. The not infrequent occurrence of consanguineous marriages and "assortative matings" in the small Jewish communities of Europe might have been factors contributing to the high incidence of inherited errors of lipid metabolism in this segment of the population.

These surveys represent an attempt to estimate the occurrence of hereditary hypercholesteremia in the population at large. The ideal material for a survey of this nature would be a completely unselected group of families representative of the general population. Since the population of New York City from which the patients were drawn is not representative of the population of the United States in regard to racial origins and environmental factors (climate, diet, occupation, etc.), it would be of great interest to assay population groups in other parts of the country, as well as in other countries, in order to obtain a more accurate estimate of this inborn error of metabolism in the general population.

ASSOCIATION OF HYPERCHOLESTEREMIA AND HYPERURICEMIA

There are similarities between the clinical manifestations of hereditary hypercholesteremia and xanthomatosis on one hand and hereditary hyperuricemia and gout on the other. In gout and in xanthomatosis only one member of the family may exhibit clinical manifestations of the disease while the remaining siblings may reveal only an elevated level of serum uric acid or cholesterol, respectively. In gout as well as in xanthomatosis the metabolic abnormalities are considered to be predisposing factors for the deposition of urates or cholesterol, respectively, in the tissues. Additional mechanisms must be functioning for the development of overt symptoms.

A study of families with hereditary hypercholesteremia for evidence of hyperuricemia revealed that approximately one-third of the patients showed both hypercholesteremia and hyperuricemia.[42] We have presented elsewhere[42] data on twenty-seven individual members of hypercholesteremic families whose serum cholesterol ranged from 250 to 870 mg. per 100 ml., average 452 mg. The uric acid concentration of the serum ranged from 2.5 to 9.4 mg. per 100 ml. Analysis of these figures revealed that one-third of these patients had hyperuricemia (levels between 6 and 9.6 mg.), one-third had levels of 5–6 mg. and the rest had levels less than 5 mg. There was no clinical evidence of gout in the persons who exhibited hyperuricemia. Wolfson[43] confirmed these observations and proposed the term "non-gouty hyperuricemia associated with familial hypercholesteremia." The coincidence of the two metabolic errors involving lipids and purines may prove of importance in future studies of the underlying mechanisms, which so far are completely obscure.

In a recent paper, Gertler et al.[44] analyzed the relation of serum uric acid to coronary heart disease; in the opinion of these authors high uric acid levels may be associated with atherosclerosis. The serum uric acid concentration was included in an expression involving the ratio of cholesterol to lipid phosphorus in the hope of obtaining a better index for separation of "the pre-coronary healthy state and the non-coronary healthy state." Although the figures presented appear to be statistically significant, confirmation in larger groups of patients would be desirable.

COMMENTS

The early studies of Schoenheimer[45] on mice led to the conclusion that cholesterol can be synthesized in the animal body. It has been well established since then that the liver can synthe-

size cholesterol from acetate.[46] This synthesis also takes place in the adrenal cortex, kidney, small intestine and testis,[47] and recently evidence was obtained that the arterial wall of the rabbit and chick can synthesize cholesterol.[48] The role of "local" cholesterol synthesis in the arterial wall as well as the importance of "dietary" and "extradietary cholesterol" in the genesis of atherosclerosis is unknown at present. Extensive discussions of the present state of knowledge of lipid metabolism in relation to atherosclerosis and of the pathology of atherosclerosis were published in two preceding seminars of this series.[11,49] Additional information may be found in previously published reviews[50–53] and articles.[54–68]

Our knowledge concerning genetic control of metabolic processes was substantially enriched by the pioneering work of Beadle and his school[69] with the pink bread mold Neurospora. It has been well established that alteration (mutation) of a single gene may result in inability to carry out a specific biologic reaction due to the loss of a specific enzyme system required for this reaction; new reactions leading to different biologic processes may thus arise. Gene mutation produced, e.g., by exposure to ultra-violet light, may cause a metabolic change leading eventually to new growth factors. The new requirement then becomes a hereditary trait since crossing of the mutant strain with the parent strain will lead to Mendelian segregation.

Thus a single gene difference between the mutant and the parental strains produces inability to synthesize certain substances, e.g., factors of the vitamin B complex or various amino acids. Evidence is available to suggest that the mechanisms of gene action are essentially similar in all living matter, and that many metabolic pathways in man are similarly controlled by genetic factors.[70,71]

The nature of the inborn error of lipid metabolism resulting eventually in hypercholesteremia and predisposition to atherosclerosis is obscure. By analogy with other inborn faults of metabolism one might suspect that in primary cholesterol lipidosis (as well as in other lipidoses), a disturbance occurs in genetically determined enzymatic chain reactions which leads to abnormal metabolic pathways and results in the accumulation of lipid substances in the blood and in the tissues. At present our knowledge of the enzymatic systems controlling synthesis and degradation of cholesterol (and other lipids) under normal and especially under pathologic conditions is very limited.[11]

A hereditary disturbance of lipid metabolism represents only one conditioning factor for the development of atherosclerosis, and many additional factors are probably involved. Among these are anatomic peculiarities, such as coronary intimal thickening in the male,[72] variations in permeability of the intima and alteration of the intercellular ground substance.[49] Time must also be considered as factor, as Anitschkow[73] noted long ago. In our own observations in hypercholesteremic families, some of the members first developed only one stigma of this genetic disorder; gradually addit onal stigmata developed and the patients died eventually of myocardial infarction.[29] Finally, the possibility that some hormonal influences may be involved must be taken into consideration although our knowledge in this field is very limited. Nevertheless, evidence is accumulating to indicate that the metabolism of lipids is subject to hormonal control in a manner similar to carbohydrate and protein metabolism. In addition to the established role of the thyroid, the adrenal cortex and the gonads seem to exert an important regulating function in lipid metabolism.[74]

SUMMARY

In the field of disturbances of lipid metabolism certain inborn errors have long been known. The genetic mechanisms involved in these disorders are summarized, with special emphasis on primary cholesterol lipidosis (xanthomatosis). Genetic analysis supports the concept that this disturbance of cholesterol metabolism is inherited as an (incomplete) dominant trait.

The abnormalities most frequently encountered in members of xanthomatous families are hypercholesteremia and coronary atherosclerosis; xanthoma, from which the name of the disorder was derived, is found least often, while xanthelasma and corneal arcus are more frequently noted. The term "cholesterol lipidosis" appears therefore to be more appropriate than "xanthomatosis" to describe this disorder.

Studies of patients with coronary atherosclerosis below the age of fifty, and their families, reveal that their disease exhibits a pattern similar to that encountered in xanthomatous families. The majority of these patients show abnormally high serum cholesterol levels. Approximately one-third to one-half of their siblings exhibit hypercholesteremia and many have, in addition, corneal arcus and xanthelasma, and a few

develop xanthoma. Genetic analysis reveals that the number of persons in these sibships presenting hypercholesteremia fits a 1:1 Mendelian ratio and that hereditary transmission occurs probably as a dominant trait.

The common denominator for most patients with early coronary atherosclerosis may be a hereditary disturbance of lipid (or lipoprotein) metabolism manifested by elevated serum cholesterol levels. Familial xanthomatosis is the most severe form of this inborn metabolic fault and coronary atherosclerosis is very frequent in such persons. They carry, we assume, two genes responsible for disturbed lipid metabolism, i.e., they are homozygotes. Uncomplicated coronary artery disease apparently represents a milder form of this same general disturbance. These persons probably carry one gene responsible for faulty lipid metabolism, i.e., they are heterozygotes.

A study of the families of 500 consecutive unselected admissions, 250 males and 250 females, to a medical ward of a large general hospital reveals an incidence of hereditary hypercholesteremia of 4 to 5 per cent. This incidence was higher than suspected. Hereditary hypercholesteremia was not encountered in the non-white segment of the hospital population although 10 per cent of the studied families belonged in this category. There is a high incidence of this inborn abnormality among Jewish families, a feature common to all disorders of lipid metabolism.

It is assumed that in primary cholesterol lipidosis, as well as in other lipidoses, a disturbance occurs in genetically determined enzymatic chain reactions. This enzymatic aberration leads to abnormal metabolic pathways and results in the accumulation of lipid substances in the blood and in the tissues.

REFERENCES

1. Garrod, A. E. Inborn Errors of Metabolism. London, 1909. Henry Frowde; 2nd ed., London, 1923. Henry Frowde & Hadder & Stoughton.
2. (*a*) Gutman, A. B. Inborn errors of metabolism. In: Cecil, R. L. and Loeb, R. F. A Textbook of Medicine. Philadelphia and London, 1951. W. B. Saunders Co.; (*b*) Thorn, G. W. Inborn errors of metabolism. In: Harrison, T. R. Principles of Internal Medicine. Philadelphia and Toronto, 1950. The Blakiston Co.
3. (*a*) Niemann, A. Ein unbekanntes Krankheitsbild. *Jahrb. f. Kinderh.*, 79: 1, 1914; (*b*) Pick, L. Ueber die lipoidzellige Splenohepatomegalie Typus Niemann-Pick als Stoffwechselerkrankung. *Med. Klin.*, 23: 1483, 1927.
4. Pfaendler, U. La maladie de Niemann-Pick dans le cadre de lipoidoses. *Schweiz. med. Wchnschr.*, 76: 1128, 1946.
5. Sachs, B. Amaurotic family idiocy and general lipoid degeneration. *Arch. Neurol. & Psychiat.*, 2: 247, 1929.
6. Knox, J. H. M., Jr., Wahl, H. R. and Schmeisser, R. Gaucher's disease; a report of two cases in infants. *Bull. Johns Hopkins Hosp.*, 27: 1, 1916.
7. Hamburger, R. Lipoidzellige Splenohepatomegalie (Typus Niemann-Pick) in Verbindung mit Amaurotischer Idiotie bei einem 14 Monate alten Maedchen. *Jahrb. f. Kinderh.*, 116: 41, 1927.
8. Freudenberg, E. Klinische Beobachtungen und Untersuchungen an einem Zwillingspaar mit Niemann-Pick'scher Krankheit (NPK). *Ztschr. f. Kinderh.*, 59: 313, 1937.
9. Klenk, E. Über die Natur der Phosphatide in der Milz bei der Niemann-Pick, schen Krankheit. *Ztschr. f. Phys. Chem.*, 229: 151, 1934.
10. Thannhauser, S. J. Lipidoses—Diseases of the Cellular Lipid Metabolism. New York, 1950. Oxford University Press.
11. Gould, R. G. Lipid metabolism and atherosclerosis. *Am. J. Med.*, 11: 209, 1951.
12. Gaucher, E. De l'epithélioma primitif de la rate. Thèse, Paris, 1882.
13. Collier, W. A. A case of enlarged spleen in a child aged six. *Tr. Path. Soc. London*, 46: 148, 1895.
14. Bovaird, D., Jr. Primary splenomegaly—endothelial hyperplasia of the spleen. Two cases in children, autopsy and morphological examination in one. *Am. J. M. Sc.*, 120: 377, 1900.
15. (*a*) Brill, N. E. Primary splenomegaly with a report of three cases occurring in one family. *Am. J. M. Sc.*, 121: 377, 1901; (*b*) Brill, N. E. and Mandlebaum, F. S. Large-cell splenomegaly (Gaucher's disease): a clinical pathological study. *Am. J. M. Sc.*, 146: 863, 1913.
16. Groen, J. Hereditary mechanism of Gaucher's disease. *Blood*, 3: 1238, 1948.
17. Gordon, G. L. Osseous Gaucher's disease. Report of two cases in siblings. *Am. J. Med.*, 8: 332, 1950.
18. Reich, C., Seife, M. and Kessler, B. J. Gaucher's disease: a review and discussion of twenty cases. *Medicine*, 30: 1, 1951.
19. Oberling, C. and Woringer, P. La maladie de Gaucher chez le nourisson. *Rev. franç. de pédiat.*, 3: 475, 1927.
20. (*a*) Chambard, E. Des formes anatomiques du xanthelasma cutané. *Ann. de dermat. et syph.*, 10: 5, 241, 1878; (*b*) Fagge, C. H. Xanthomatous diseases of the skin: I. general xanthelasma or vitiligoidea. *Tr. Path. Soc. London*, 24: 242, 1873.
21. (*a*) Addison, T. and Gull, W. On a certain affection of the skin, vitiligoidea—(a) plana; (b) tuberosa with remarks. *Guy's Hosp. Rep.*, 7: 265, 1851; (*b*) Pick, L. and Pinkus, F. Ueber doppelbrechende Substanz in Hauttumoren, ein Beitrag zur Kenntniss der Xanthome. *Monatsch. f. prakt. Dermat.*, 5: 46, 1908; Weitere Untersuchungen zur Xanthomfrage; die echten xanthomatoesen Neubildungen. *Dermat. Ztschr.*, 36: 1827, 1909; Weitere Mitteilungen zur Lehre von den Xanthomen. *Arch. f. Dermat. u. Syph.*, 99: 465, 1910.
22. Gossage, A. M. The inheritance of certain human abnormalities. *Quart. J. Med.*, 1: 331, 1908.

23. Lane, G. C. and Goodman, J., Jr. Xanthoma tuberosum. *Arch. Dermat. & Syph.*, 32: 377, 1935.
24. Sperry, W. M. and Schick, B. Essential xanthomatosis: treatment with cholesterol free diet in two cases. *Am. J. Dis. Child.*, 51: 1372, 1936.
25. (*a*) Mueller, C. Xanthomata, hypercholesteremia, angina pectoris. *Acta med. Scandinav.* (*suppl.*), 89: 75, 1938; (*b*) Mueller, C. Angina pectoris in hereditary xanthomatosis. *Arch. Int. Med.*, 64: 675, 1939.
26. Thannhauser, S. J. and Magendantz, H. The different clinical groups of xanthomatous diseases, a clinical physiological study of 22 cases. *Ann. Int. Med.*, 11: 1662, 1938.
27. Thannhauser, S. J. and Schmidt, G. Lipins and lipidoses. *Physiol. Rev.*, 26: 275, 1946.
28. Boas, E. P. and Adlersberg, D. Familial hypercholesteremia (xanthomatosis) and atherosclerosis. *J. Mt. Sinai Hosp.*, 12: 84, 1945.
29. Boas, E. P., Parets, A. D. and Adlersberg, D. Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis. *Am. Heart J.*, 35: 611, 1948.
30. Svendsen, M. Are supernormal cholesterol values in serum caused by a dominantly inherited factor? *Acta med. Scandinav.*, 104: 235, 1940.
31. Bloom, D., Kaufman, S. R. and Stevens, R. A. Hereditary xanthomatosis. *Arch. Dermat. & Syph.*, 45: 1, 1942.
32. Adlersberg, D., Parets, A. D. and Boas, E. P. Genetics of atherosclerosis: studies of families with xanthoma and unselected patients with coronary artery disease under the age of fifty years. *J. A. M. A.*, 141: 246, 1949.
33. Wilkinson, C. F., Jr., Hand, E. A. and Fliegelman, M. T. Essential familial hypercholesteremia. *Ann. Int. Med.*, 29: 676, 1948.
34. Montgomery, H. Cutaneous manifestations of diseases of lipoid metabolism. *M. Clin. North America*, 24: 1249, 1940.
35. (*a*) Harbitz, F. Xanthomatosis as cause of sudden death. *Norsk mag. f. Lægevidensk.*, 97: 695, 1936; (*b*) Harbitz, F. Sudden death of young persons from "natural" (non-violent) causes and its medicolegal significance. *Norsk mag. f. Lægevidensk.*, 99: 1250, 1938.
36. Klatskin, G. Familial xanthomatosis and arcus senilis. *Internat. Clin.*, 3: 13, 1941.
37. Boas, E. P. Arcus senilis and arteriosclerosis. *J. Mt. Sinai Hosp.*, 12: 79, 1945.
38. Stecher, R. M. and Hersh, A. H. Note on the genetics of hypercholesteremia. *Science*, 109: 61, 1949.
39. (*a*) Adlersberg, D., Schaefer, L. E., Drachman, S. R. and Dritch, R. Incidence of hereditary hypercholesteremia. *Circulation*, 2: 475, 1950 (abstr.); (*b*) idem. Incidence of hereditary hypercholesteremia. (To be published.)
40. Adlersberg, D., Drachman, S. R. and Schaefer, L. E. Further studies on the incidence of hereditary hypercholesteremia. (To be published.)
41. Wilkerson, H. L. G. and Krall, L. P. Diabetes in a New England town. A study of 3,516 persons in Oxford, Mass. *J. A. M. A.*, 135: 209, 1947.
42. Adlersberg, D. Newer advances in gout. *Bull. New York Acad. Med.*, 25: 651, 1949.
43. Wolfson, W. Q. Personal communication.
44. Gertler, M. M., Garn, S. M. and Levine, S. A. Serum uric acid in relation to age and physique in health and in coronary heart disease. *Ann. Int. Med.*, 34: 1421, 1951.
45. Schoenheimer, R. and Breusch, F. Synthesis and destruction of cholesterol in the organism. *J. Biol. Chem.*, 103: 439, 1933.
46. (*a*) Bloch, K. and Rittenberg, D. An estimation of acetic acid formation in the rat. *J. Biol. Chem.*, 159: 45. 1945; (*b*) Bloch, K., Berek, E. and Rittenberg, D. Synthesis of cholesterol in surviving liver. *J. Biol. Chem.*, 162: 441, 1946.
47. (*a*) Svere, P. A., Chaikoff, I. L. and Dauben, W. G. The in vitro synthesis of cholesterol from acetate by surviving adrenal tissue. *J. Biol. Chem.*, 176: 829, 1948; (*b*) Svere, P. A., Chaikoff, I. L., Treitmann, S. S. and Burstein, L. S. The extrahepatic synthesis of cholesterol. *J. Biol. Chem.*, 182: 629, 1950.
48. Siperstein, M. D., Chaikoff, I. L. and Chernick, S. S. Significance of endogenous cholesterol in arteriosclerosis: synthesis in arterial tissue. *Science*, 113, 747, 1951.
49. Duff, G. L. and McMillan, G. C. Pathology of atherosclerosis. *Am. J. Med.*, 11: 92, 1951.
50. Anitschkow, N. In: Cowdry, E. V. Arteriosclerosis: —a survey of the problem. Chapt. 10. New York, 1933. Macmillan Co.
51. Hueper, W. C. Arteriosclerosis. *Arch. Path.*, 39: 187, 1945.
52. Katz, L. N. and Dauber, D. V. Pathogenesis of atherosclerosis. *J. Mt. Sinai Hosp.*, 12: 382, 1945.
53. Gubner, L. and Ungerleider, H. E.: Arteriosclerosis: a statement of the problem. *Am. J. Med.*, 6: 60, 1949.
54. (*a*) Duff, G. L. and McMillan, G. C. The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. I. The inhibition of experimental cholesterol atherosclerosis in alloxan diabetes. II. The effect of alloxan diabetes on the retrogression of experimental cholesterol atherosclerosis. *J. Exper. Med.*, 89: 611, 1949; (*b*) Duff, G. L. and Payne, T. P. B. The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. III. The mechanism of the inhibition of experimental cholesterol atherosclerosis in alloxan-diabetic rabbits. *J. Exper. Med.*, 92: 299, 1950.
55. Kellner, A., Correll, J. W. and Ladd, A. T. The influence of intravenously administered surface-active agents on the development of experimental atherosclerosis in rabbits. *J. Exper. Med.*, 93: 385, 1951.
56. Payne, T. P. B. and Duff, G. L. The effect of tween 80 on the serum lipids and the tissues of cholesterol-fed rabbits. *Arch. Path.*, 51: 379, 1951.
57. (*a*) Gertler, M. M., Garn, S. M. and Bland, E. F. Age, serum cholesterol and coronary artery disease. *Circulation*, 2: 517, 1950; (*b*) Gertler, M. M. and Garn, S. M. Lipid interrelationship in heart and coronary artery disease. *Science*, 112: 14, 1950.
58. Katz, L. N. Newer approaches to the pathogenesis of atherosclerosis. Presented before the section on

Internal Medicine, Annual Session of the A. M. A. in Atlantic City, N. J., Friday, June 15, 1951.

59. (*a*) Gofman, J. W., Lidgren, F., Elliott, H., Mantz, W., Hewitt, J., Strisower, B. and Herring, V. The role of lipids and lipoproteins in atherosclerosis. *Science*, 111: 167, 1950; (*b*) Gofman, J. W. et al. Blood lipids and human atherosclerosis. *Circulation*, 2: 161, 1950.
60. Review. Atherosclerosis, serum cholesterol, and lipoproteins. *Nutrition Rev.*, 9: 167, 1951.
61. Keys, A. Cholesterol, giant molecules and atherosclerosis. Presented before the Section on Internal Medicine. Annual Session of A. M. A. in Atlantic City, N. J., Friday, June 15, 1951.
62. Keys, A., Mickelson, O., Miller, E. V. O. and Chapman, C. B. The relation in man between cholesterol levels in the diet and in the blood. *Science*, 112: 79, 1950.
63. Hildreth, E. A., Melinkoff, S. M., Blair, G. W. and Hildreth, D. M. The effect of vegetable fat ingestion on human serum cholesterol concentration. *Circulation*, 3: 641, 1951.
64. Messinger, W. J., Porosowska, W. and Steele, J. M. Effect of feeding egg yolk and cholesterol on serum cholesterol levels. *Arch. Int. Med.*, 86: 189, 1950.
65. Dock, W. The causes of arteriosclerosis. *Bull. New York Acad. Med.*, 26: 182, 1950.
66. Snapper, I. Clinical lessons to Western Medicine: A contribution to Geographical Medicine from the Clinics of Peiping Union Medical College, New York, 1941. Interscience Publishers, Inc.
67. (*a*) Aschoff, L. Lectures on Pathology. New York, 1924. Paul B. Hoeber; (*b*) Wilens, S. L. Bearing of general nutritional state on atherosclerosis. *Arch. Int. Med.*, 79: 129, 1947.
68. Dock, W. Arteriosclerosis. In: Harrison, T. R. Principles of Internal Medicine, Philadelphia and Toronto, 1950. The Blakiston Co.
69. (*a*) Beadle, G. W. Genetic control of biochemical reactions. *Harvey Lect.* (1944–1945), 40: 179, 1945. (*b*) Bonner, D. M. Combined staff clinics: inborn errors of metabolism. *Am. J. Med.*, 8: 90, 1950.
70. (*a*) Neuberger, A., Rimington, C. and Wilson, J. M. G. Quoted in combined staff clinics: inborn errors of metabolism. *Am. J. Med.*, 8: 90, 1950; (*b*) Levine, S. Z. Tyrosine and phenylalanine metabolism in infants and the role of vitamin C. *Harvey Lect.* (1946–1947), 42: 303, 1947.
71. Mason, H. H. and Turner, M. E. Chronic galactemia. Report of case with studies on carbohydrates. *Am. J. Dis. Child.*, 50: 359, 1935.
72. Dock, W. The predilection of atherosclerosis for the coronary arteries. *J. A. M. A.*, 131: 875, 1946.
73. Anitschkow, N. In: Cowdry, E. V.,[50] p. 309.
74. (*a*) Adlersberg, D., Schaefer, L. E. and Dritch, R. Adrenal cortex and lipid metabolism: effects of cortisone and adrenocorticotropin (ACTH) on serum lipids in man. *Proc. Soc. Exper. Biol. & Med.*, 74: 877, 1950; (*b*) Adlersberg, D., Schaefer, L. E. and Drachman, S. R. The development of hypercholesteremia during cortisone and ACTH therapy. *J. A. M. A.*, 144: 909, 1950; (*c*) Adlersberg, D., Schaefer, L. E. and Drachman, S. R. Studies on hormonal control of serum lipid partition in man. *J. Clin. Endocrinol.*, 11: 67, 1951; (*d*) Steiner, A. and Kendall, F. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946; (*e*) Stamler, J., Silber, E. N., Miller A. J., Akman, L., Bolene, C. and Katz, L. N. Effect of thyroid and dinitrophenol on induced hypermetabolism on plasma and tissue lipids in the cholesterol-fed chick. *J. Lab. & Clin. Med.*, 35: 351, 1950.

Research Society Abstracts

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING IN NEW ORLEANS, LOUISIANA, JANUARY 26, 1951

THE PROBLEM OF RENAL VASCULAR SHUNTS. *John H. Moyer, M.D. and Carroll A. Handley, Ph.D.* (From the Departments of Medicine and Pharmacology, Baylor University College of Medicine, Houston, Tex.)

Morphologic studies and direct renal blood flow determinations have failed to support the hypothesis that renal arteriovenous shunts become activated following neurogenic and circulatory stress. This problem has been studied in dogs following hemorrhage and two hours of sciatic nerve stimulation. Renal plasma flow (PAH), glomerular filtration rate (creatinine), and oxygen extraction determinations were done. The renal vein was catheterized under fluoroscopic guidance. If arteriovenous shunts are of any significance, the filtration fraction should decrease as well as the extraction of p-aminohippurate and oxygen.

There were no instances of significant decrease in PAH extraction whereas the oxygen extraction either increased or did not change. The renal plasma flow decreased in two-thirds of the animals. This was accompanied by increasing filtration fractions. In the remaining dogs there was no discernible alteration of renal function. Hemorrhage accentuated these alterations. The findings are interpreted to indicate that under the conditions of the experiment, neurogenic reflexes, which decrease total renal blood flow, have become activated. However, there is no evidence to support the existence of intrarenal arteriovenous shunts or by-passes. Renal clearance studies on seven patients with acute anuria seem to support these findings.

EFFECT OF EXERCISE ON SODIUM EXCRETION IN NORMAL AND CARDIAC SUBJECTS. *Francis W. Fitzhugh, M.D., Ralph A. Huie, Jr., M.D. and Arthur J. Merrill, M.D.* (From the Department of Medicine, Emory University School of Medicine and the Medical Service, Grady Hospital, Atlanta, Ga.)

Previous studies have compared the effects of exercise upon the renal plasma flow and filtration rate in cardiac and normal subjects. The greater reduction in filtration rate in the cardiac patients was explained by their inability to increase cardiac output in proportion to tissue demand. Cardiac patients who are compensated at bed rest often have failure as a result of prolonged and severe exertion. The comparatively greater fall in filtration rate associated with exercise in cardiac subjects was offered as a cause for the relatively greater salt and water retention by these individuals with exercise.

This concept has been questioned by others who have demonstrated a diminution in sodium excretion with exercise in normals almost equal to that found in cardiacs. Furthermore, they found this to occur at times without any reduction in filtration rate.

The present report deals with data from six non-cardiac and two cardiac subjects employing hippurate and inulin clearances, with sodium excretion determinations. In no case did sodium excretion fall with exercise without a definite decrease in filtration rate. This is important in clarifying our concept of edema formation in these patients.

ELECTROLYTE THERAPY IN CHRONIC RENAL DISEASE. *Reno R. Porter, M.D., Richard A. Neubauer, M.D., Ernst Fischer, M.D. and Nelson F. Young, Ph.D.* (From the Medical College of Virginia, Richmond, Va.)

Until recently the administration of sodium or potassium to patients with chronic renal disease has been considered contraindicated except for replacement therapy in either salt- or potassium-losing nephritides which are relatively uncommon. However, in most cases of chronic renal disease there is lowered serum sodium and acidosis, and Fox has demonstrated an intracellular deficit of potassium. We have demonstrated in muscle analyses on human beings that there is a moderate excess of sodium and a marked excess of chloride in whole muscle in these cases. Since Pitts noted that excess bicarbonate will favor chloride excretion, the use

of sodium and potassium acetate in such cases appeared to be rational therapy. This method of treatment has been used in one case of terminal uremia and two cases of nephrotic stage of chronic glomerulonephritis, with clinical improvement in each case. Balance data indicate that this improvement is associated with a marked negative chloride balance, the amount of chloride excreted being in excess of what could be expected to come from the extracellular space. Further, there was a positive potassium balance and, in addition, the cases of nephrosis showed negative sodium and water balances.

Effect of a New Cation Exchange Resin on Edematous States and Electrolyte Balance. *F. Carter Pannill, M.D., Don W. Chapman, M.D. and Ray H. Skaggs, M.D.* (From the Department of Medicine, Baylor University College of Medicine, Houston, Tex.)

Since salt-poor diets are notably unpalatable, the possibility of using a new cation exchange resin to eliminate excess sodium in the diet was investigated. Fourteen subjects, including two normals as well as cardiacs, nephritics and patients with portal cirrhosis were studied. All had relatively normal kidney function. A constant diet containing 6 gm. of salt was administered and the effects of cation exchangers (carboxylic acid and potassium resins) on electrolyte balance were studied. Daily determinations of serum sodium and potassium levels and twenty-four-hour urinary sodium, potassium excretions were made. Blood chlorides, calcium, carbon dioxide combining power, electrocardiographic tracings, blood urea nitrogen and total base determinations were obtained at frequent intervals over a two-week period, as well as frequent weighing of the patients.

Serum potassium, calcium and chloride levels tended to remain within normal limits. In some there was a reduction in the serum sodium levels. Urinary sodium excretion was greatly reduced while urinary potassium excretion was increased. No appreciable change in the electrocardiographic tracings occurred nor was there a change in the total blood base. Edematous patients showed progressive weight loss; some losing as much as 20 to 25 pounds. Fecal sodium output was found to be markedly increased while the patients were on the cation exchangers.

No untoward side reactions were observed in these patients and their appetites remained good throughout the period. By the addition of the potassium resin the hazard of potassium depletion was apparently eliminated.

Protective Effect of Ascorbic Acid against the Depression of Respiration of Rat Heart and Kidney Slices by Mercuhydrin. *A. Ruskin, M.D., B. Ruskin, M.S. and W. Nowinski, Ph.D., Galveston, Tex.*

We have previously shown that mercuhydrin depresses the oxygen uptake of rat heart and kidney slices and that this effect is due to the mercurial and not the aminophylline fraction. Ascorbic acid has been shown to protect the heart against the toxic effects of mercuhydrin and other mercurials. It was found that ascorbic acid restores the mercuhydrin—depressed oxygen uptake of rat kidney slices if the ascorbic acid is added in the approximate molar concentration ratio of one to three of mercuhydrin.

Controls with different amounts of ascorbic acid and tissue showed no difference in the oxygen uptake. Under experimental conditions no spontaneous oxidation of ascorbic acid takes place. Preliminary work with heart slices shows similar effects.

It is possible that ascorbic acid protects the sulfhydryl enzymes against inactivation by the mercurial fraction of mercuhydrin, and that this is indirectly shown by the effects of the individual and combined drugs upon the respiration of rat tissue slices.

Drug Therapy of Hypertension. *Clayton R. Sikes, M.D. and J. Gordon Barrow, M.D.* (From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.)

Patients selected for the study were examples of uncomplicated essential hypertension. The drugs employed included an adrenolytic agent (C-7337), a purified veratrum alkaloid (V-056–11) and a mixture of three dehydrogenated ergot alkaloids (CCK-179).

C-7337, given intravenously, is a potent hypotensive agent in doses of 20 to 60 mg. Given orally the drug is unsatisfactory because of unpleasant side effects and rapid tachyphylaxis.

V-056-11, given orally, produced a definite hypotensive effect in only 20 per cent of the patients. Unpleasant side effects were frequent even with careful regulation of the dosage.

CCK-179 was found to be non-toxic. In an occasional patient it produced striking results, but less than half the patients had a definite fall in blood pressure. Each patient was controlled by placebo administration. The study of this drug is being extended over longer periods so

that its effect on the course of the hypertensive vascular disease can be ascertained.

IMIDAZOLINE AS A HYPOTENSIVE AGENT. *Coleman D. Caplovitz, M.D. and John H. Moyer, M.D.* (From the Baylor University College of Medicine, Houston, Tex.)

Imidazoline (the hydrochloride salt of 2-(N, p-tolyl-N-(m′oxy-phenyl)-amino-methyl)-imidazoline) was investigated as a potential hypotensive agent in sixteen hypertensives. In all patients the intravenous or intramuscular administration of 1 or 2 mg. per kg. of the drug resulted in significant fall in blood pressure and moderate to severe postural hypotension. The mean fall in systolic pressures in the supine position was 38 mm. of mercury and in diastolic pressures 35 mm., occurring in approximately fifteen minutes. In the erect position, mean systolic fall was 89 mm. and mean diastolic fall 60 mm. The duration of response varied from forty minutes to several days. Side reactions occurred in fourteen patients and consisted of tachycardia, palpitation, a hot flushed feeling, cough, dyspnea, stuffiness of the nose, diaphoresis, nausea, weakness, dizziness and somnolence.

Imidazoline was administered orally in doses of 30 to 120 mg. three to five times a day to eleven of the sixteen patients. Of these, five patients demonstrated slight to moderate postural hypotension and two had a drop in their reclining pressures. Three patients developed gastrointestinal symptoms (cramps and diarrhea, nausea and vomiting) necessitating cessation of oral therapy, and three others developed similar but milder symptoms. Five patients had no gastrointestinal side effects.

From preliminary study it would seem that side effects will tend to limit the use of imidazoline to the severe hypertensive crises.

RESPONSE OF PATIENTS WITH CONGESTIVE HEART FAILURE TO ACUTE ELEVATION OF TEMPERATURE AND HUMIDITY. *G. S. Berenson, M.D.* (From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans, La.)

Observations were made to investigate the intolerance of patients with cardiac disease and congestive heart failure to stress of a hot and humid environment. Thirteen patients in various stages of congestive failure were studied and compared with thirteen control subjects. In three experiments one control subject and one patient with congestive failure were studied simultaneously. Following observations in comfortable atmospheric conditions, response to a hot and humid atmosphere (40 ± 2°C., 85 per cent relative humidity) for periods of 40 to 114 minutes was noted.

The heated surroundings precipitated acute attacks of "left ventricular failure" (cardiac asthma) characterized by severe dyspnea, orthopnea and pulmonary rales, associated with apprehension in five subjects with cardiac disease. Gallop rhythm developed or was accentuated in nine patients. Ability to withstand stress of a hot, humid environment was definitely less in subjects with congestive heart failure. This group exhibited primarily cardiovascular and pulmonary intolerance, whereas many central nervous system disturbances developed in the controls who were able to endure sufficiently prolonged exposures to the environment. The cardiovascular reactions in control subjects tended to be more uniform and were characterized especially by elevation of pulse pressure.

These experiments indicate the intolerance of patients with certain types of cardiac disease to a hot and humid atmosphere and also suggest need for control of environmental atmosphere during therapy.

EFFECTS OF PARITOL ON THE PROTHROMBIN TIMES, ANTI-THROMBIN TIMES AND LEE-WHITE CLOTTING TIMES. *Alan A. Ory, M.D. and Don W. Chapman, M.D.* (From the Department of Medicine, Baylor University College of Medicine, Houston, Tex.)

Of twenty-three dogs studied the following results were observed: (1) Paritol A in doses of 5 mg. per kg. of body weight was the most effective dose, giving a peak effect in fifteen to thirty minutes with prolongation of the Lee-White clotting time to twice or three times the normal value for four to five hours. (2) The prothrombin time, as measured by the Link-Shapiro modification of Quick's method may be notably prolonged by Paritol. (3) Protamine sulfate effects a prompt return of the clotting time to normal.

Sixteen patients including three controls have been treated with Paritol C for twenty-four to seventy-two hours with an average of fifty hours without any demonstrable toxic effects or developments of clinical thrombosis or emboli. Patients initially received a dose of 5 mg. per kg. of Paritol C intravenously and 3 to 5 mg. per kg. when the clotting time fell below twenty minutes. The clotting time was

effectively prolonged to ten hours with extremes of eight to twelve hours. Five required additional Paritol C only at twelve-hour intervals. In eight the prothrombin time was appreciably prolonged. In two the prothrombin time dropped from 90 per cent to 10 per cent of normal within twenty-four hours. Serial prothrombin times revealed an almost immediate prolongation with a maximum peak at the end of three to four hours. Similarly, the anti-thrombin activity was greatly increased immediately following the administration of Paritol C.

EFFECT OF THE INTRAVENOUS ADMINISTRATION OF DEXTRAN ON CARDIAC OUTPUT AND OTHER CIRCULATORY DYNAMICS. *A. C. Witham, M.D., J. W. Fleming, M.D. and W. L. Bloom, M.D.* (From the Research Section, Lawson VA Hospital, Chamblee, Ga.)

It has been well established that partially hydrolyzed dextran is effective in expanding and maintaining the blood volume. There have been conflicting reports concerning the ability of increased blood volume to enhance consistently the cardiac output in normal subjects, but these have utilized saline and albumin administration.

The use of isotonic 6 per cent dextran solution and the dye dilution technic for cardiac output (Hamilton) provided an opportunity to study effects of blood volume expansion on the pulmonary circulation as well as the cardiac output and other hemodynamics. Five normal men were given 500 cc. of 6 per cent dextran. Pulmonary artery and femoral artery pressures were followed and cardiac output determinations were made before and after dextran administration. The data show that this preparation of dextran consistently increased the blood volume proportionately to the amount administered and that the effect was prolonged. Cardiac output was increased in every case. The increased blood volume was associated with prolonged elevations of pressure in the pulmonary artery.

STUDIES ON THE GASTROINTESTINAL EXCRETION OF DEXTRAN. *Napier Burson, Jr., M.D. and Walter L. Bloom, M.D.* (From the Research Section of Lawson VA Hospital, Chamblee, Ga.)

Only a portion (30 to 50 per cent) of dextran injected intravenously is excreted in the urine. Since there is no evidence that it is metabolized or stored, its possible excretion into the gastrointestinal tract has been suggested. Using the Hint-Thorsen method of dextran determination, Engstrand and Aberg indicated that appreciable amounts of dextran are excreted into the lumen of the gut in normal subjects, in humans with intestinal obstruction and in animals with artificial intestinal obstruction.

Studies in our laboratory using the Bloom-Willcox method of dextran determination have shown insignificant amounts of dextran in the gut following its intravenous administration in a 6 per cent solution. These determinations have been made on specimens obtained from the stomach, duodenum, various levels in the jejunum and ileum, and the common bile duct of human subjects with no gastrointestinal or renal disease.

ANALYSIS OF VECTORCARDIOGRAMS BY HIGH-SPEED MOTION PICTURES. *C. E. Jackson, M.D., J. A. Abildskov, M.D., G. E. Burch, M.D. and J. A. Cronvich, M.S.* (From the Department of Medicine, Tulane University School of Medicine, New Orleans, La.)

For detailed analysis of the vectorcardiogram as inscribed on the cathode-ray oscilloscope, we have employed an Eastman high-speed 16 mm. camera with a 63 mm. f/2.7 coated lens. Satisfactory results were obtained with the use of Eastman Cine-Kodak Super XX film, with high cathode-ray beam intensity. The P1 medium-persistence green screen on the cathode-ray oscilloscope was more satisfactory than the P7 long-persistence screen which produced a brighter image but did not leave a "trail" because its yellow afterglow was not sufficiently intense to be photographed. This "trail" is of value in the movie analysis of the vectorcardiogram.

A movie shows frontal and sagittal views of the vectorcardiogram of an individual with right bundle branch block taken at camera speeds of 240 to 1,600 frames per second. Speeds up to 3,200 frames per second have been used, however. When projected at 16 frames per second, films taken at 1,600 frames per second present a temporal magnification of 100 times the actual electrical event.

Features of note observed in the film include the irregular course of the trace during the initial stages of ventricular repolarization. This is consistent with the electrocardiographic theory which supposes this process to begin irregularly in many parts of the heart. The film illustrates the fact that electrical processes may

be occurring in one plane of the body while little change is observed in other planes.

CLINICAL USE OF THE PROTEIN-BOUND IODINE DETERMINATION IN A GENERAL HOSPITAL. *Philip K. Bondy, M.D. and Bernard L. Hallman, M.D.* (From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.)

The development of a simple method (Barker and Humphrey) for the PBI determination has made this test available for routine hospital practice. The method has been used for over 1,700 determinations in the past year. Normal values fall between 3.4 and 7.8 mcgm./100 ml. of serum. The value is elevated in hyperthyroidism and after the injection of iodine-containing compounds. It is depressed in hypothroidism. It is particularly useful in the diagnosis of cases (e.g., heart disease, fever, anxiety and psychosis) in which the BMR is misleading. In certain patients the diagnosis can be made only by use of the PBI. Antithyroid medication causes an immediate fall of the PBI, with a slower fall of the BMR. The PBI therefore confirms the adequacy of antithyroid dosages but does not indicate that the metabolism has returned to normal. The clinical disadvantages of the PBI arise chiefly from falsely elevated levels caused by contamination. After pyelograms the PBI is elevated for one to two months; gallbladder dyes cause a spurious elevation for up to six months. The PBI has proved to be a valuable addition to the diagnostic armamentarium.

USE OF ACTH AND CORTISONE IN THE PREPARATION OF PATIENTS FOR OPERATIVE STRESS. *Laurence H. Kyle, M.D., William P. Walsh, M.D. and Paul D. Doolan, M.D.* (From the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.)

One patient with panhypopituitarism, prepared with testosterone and given large amounts of cortical hormone at the time of craniotomy, tolerated the operation well and demonstrated an adequate but brief catabolic response. Another patient with pituitary insufficiency was given ACTH for eight days prior to abdominal exploration. Although there occurred marked eosinopenia and a moderate rise in urinary 17-ketosteroids, there was no appreciable increase in urinary nitrogen excretion during ACTH therapy or following surgery. One patient with Addison's disease complicated by pregnancy underwent a normal uneventful delivery after treatment with cortisone and adrenocortical hormone. In one patient with severe hypoglycemia due to hyperinsulinism the administration of ACTH for four days before operation was associated with a rise of blood sugar to normal levels and a significant decrease in blood glutathione levels.

These patients are presented as examples of the value of hormonal therapy in such conditions as permit logical application on the basis of sound physiologic facts.

ELECTROENCEPHALOGRAPHIC ABNORMALITIES IN PATIENTS WITH LIVER DISEASE. *Robert A. Wise, M.D., Robert D. Westphal, M.D. and Peter E. Kellaway, Ph.D.* (From Baylor University College of Medicine, Department of Medicine, Houston, Tex.)

This study was undertaken to determine if the electroencephalogram would reveal evidence of liver dysfunction that was not evident clinically. It is not unknown for severe liver cell destruction to come to the doctor's attention because of mental symptoms, without jaundice. Electroencephalograms were made in twenty-two cases at the height of their jaundice and repeated when either the liver function tests improved or when the clinical states improved. Eight of eleven cases of cirrhosis showed definite abnormality, three were questionably abnormal, and these electroencephalographic abnormalities remained about constant in spite of clinical and laboratory improvement. Two of six cases of viral hepatitis were definitely abnormal, one clearing with recovery and the other persisting; three of the six were normal and one of the six was borderline. One case of cardiac cirrhosis was normal. Two cases of odstructive jaundice were normal. One of two cases of fatty liver was abnormal and the other borderline.

This work shows that bilirubin elevation is not a factor in causation of electroencephalographic abnormalities; that when the sensorium is grossly abnormal, the electroencephalogram is also; that when the patient's sensorium is clear, the electroencephalogram may be abnormal; and that no single liver function test can be correlated with the electroencephalogram.

EPIDEMIC OF ASEPTIC MENINGITIS DUE TO LEPTOSPIRA POMONA. *Morris Schaefier, M.D.* (From the Communicable Disease Center, Virus and Rickettsia Section, Montgomery, Ala.)

This report, to our knowledge the first of its kind in the United States, deals with an epidemic of leptospirosis wherein aseptic meningitis

was the predominant clinical feature. Sporadic cases of this type of infection (swineherd's disease) have been recognized and reported abroad on many occasions.

The outbreak occurred in a rural area in southern Alabama and involved about fifty of approximately eighty people, mostly adolescents and young adults, who had been in swimming in a commonly frequented swimming hole, on July 4, 1950. A dead hog was reported to have been seen in the creek previously. Within several days to two weeks these individuals began to come down in rapid succession with fever, headache, nausea, myalgia, arthralgia and stiff necks and backs. In some, conjunctivitis was prominent and in a few transient maculopapular rashes were observed. None had jaundice. Spinal fluid findings in about six examined were compatible with the clinical signs of aseptic meningitis. From twenty-two of these patients paired serum specimens were obtained and tested against all of the available viral and rickettsial antigens, with negative results. However, the majority showed marked rises in antibody titers against L. pomona and less significant ones against other leptospira strains. Controls of similar age and locality distribution, but not ill at this period, were negative.

AUREOMYCIN AND TERRAMYCIN IN TREATMENT OF AMEBIC COLITIS. *Eugene Brown, M.D., E. Napier Burson, M.D. and John C. Ransmeier, M.D.* (From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.)

Aureomycin was used in four patients with amebic colitis and in three asymptomatic cyst passers. Terramycin was administered to five patients with colitis and to two cyst passers. The dosage in most cases was 0.75 gm. orally every six hours for ten days. The stools usually became free of amebas on the third or fourth day of treatment, with subsidence of diarrhea and cramping. Proctoscopy revealed rapid healing of lesions in the rectosigmoid.

One amebic colitis patient relapsed a month after treatment elsewhere with aureomycin 1.5 gm. daily for one week. He was retreated with aureomycin 23.5 gm. in eight days. Another relapse occurred two months later but responded to a course of 31 gm. in ten days. The patient was free of symptoms and amebas when reexamined six and one-half months later.

Ten patients were observed from three and one-half to fourteen months following treatment. Except for the case described above, stools remained negative for E. histolytica. Giardia lamblia and H. nana, however, were not eliminated. The remaining four patients had negative stools five, fourteen, fifteen and thirty days after treatment.

Long remissions can be achieved in most patients with amebic colitis by aureomycin or terramycin therapy, and cysts are readily eliminated. We have as yet observed no relapse after administering 3 gm. of either drug daily for ten days.

LABORATORY AND CLINICAL STUDIES ON TERRAMYCIN. *Ellard M. Yow, M.D. and Daniel E. Jenkins, M.D.* (From the Department of Medicine, Baylor University College of Medicine, Houston, Tex.)

Fifty patients with infections of varied etiology were treated with terramycin. The *in vitro* sensitivity of the etiologic agents to terramycin was correlated with the therapeutic results. The response of infections due to gram-negative bacilli, lymphogranuloma venereum, granuloma inguinale and intestinal amebiasis was comparable to that obtained with aureomycin therapy. Occasionally relapses occurred following cessation of terramycin therapy in gram-positive coccal infections. Staphylococci and streptococci frequently persisted in cultures of the sputum and urine during terramycin therapy.

When a leukocytosis was associated with infection due to terramycin-sensitive organisms, the leukocyte count usually returned to normal precipitously after the institution of therapy. A transient relative increase in eosinophils was frequently noted during the administration of the antimicrobial agent.

SPECIFIC ANTISERUM AGAINST ERYTHROCYTES FROM SICKLE CELL ANEMIA; ITS USE FOR DIFFERENTIATION OF SICKLE CELL ANEMIA FROM SICKLE CELL TRAIT. *Rose G. Schneider, Ph.D. and William C. Levin, M.D.* (From the Department of Internal Medicine, University of Texas, Medical Branch, Galveston, Tex.)

Washed erythrocytes from two individuals with sickle cell anemia were injected into rabbits, and the resulting antisera were absorbed with erythrocytes of the appropriate blood group and type. The antiserum was tested against erythrocyte suspensions from twenty-four individuals with sickle cell anemia, thirty-two with sickle cell trait and 148 normal individuals. The erythrocyte suspensions from all of the

twenty-four subjects with sickle cell anemia were agglutinated by the serum; but none of the suspensions from the subjects with sickle cell trait or from the 148 normal subjects was agglutinated.

The agglutinin was readily absorbed by erythrocytes from patients with sickle cell anemia but not by erythrocytes from individuals with sickle cell trait.

The use of specific antisera against sickle cell anemia erythrocytes seems to offer a promising diagnostic aid to differentiate between the trait and the anemia, particularly in those cases in which sickle cell trait is complicated by an anemia and clinical differentiation is difficult.

NITROGEN AND PHOSPHORUS METABOLISM IN PERNICIOUS ANEMIA DURING REMISSION INDUCED BY CRYSTALLINE VITAMIN B_{12}. *G. Watson James, III, M.D. and Lynn D. Abbott, Jr., Ph.D.* (From the Department of Medicine, Medical College of Virginia, Richmond, Va.)

Four previously untreated patients with pernicious anemia were maintained on an adequate constant diet and, following a suitable control period, parenteral crystalline vitamin B_{12} was administered to investigate the effects of this substance on nitrogen and phosphorus metabolism. These observations were correlated with the clinical and hematologic response for twelve to nineteen days after beginning treatment.

All patients were maintained in positive nitrogen balance after treatment was begun; and when negative nitrogen balance existed during the control period, it promptly became positive. Increments in total circulating hemoglobin from 18 to 37 gm. per day over an average period of eleven days were observed. Nitrogen required for this one protein alone equalled or exceeded the total dietary nitrogen retained. A tendency to reduced fecal nitrogen following treatment suggested increased absorption.

The following sequence of biochemical changes was observed: first, a prompt and striking decrease in urinary phosphorus which preceded any change in the reticulocyte count; second, increased excretion of uric acid during the upswing of reticulocytes; and third, increased urine phosphorus during the period of greatest reticulocytosis.

These clinical observations suggest that vitamin B_{12} modifies a disturbance in erythrocytosis through a profound influence on nucleoprotein synthesis in the megaloblast.

TRIETHYLENE MELAMINE IN THE TREATMENT OF CERTAIN LYMPHOMAS AND LEUKEMIAS. *O. W. Burtner, M.D. and Louis C. Jensen, Jr., M.D., Coral Gables, Fla.*

The oral administration of triethylene melamine (TEM), a compound chemically related to nitrogen mustard (HN_2), will induce temporary clinical improvement in Hodgkin's disease, myelogenous leukemia and lymphatic leukemia. Experience thus far indicates that TEM produces beneficial effects similar to those obtained with HN_2. In addition, TEM appears to possess several important therapeutic advantages over the older nitrogen mustard. Triethylene melamine may be given by the oral route with little or no nausea, thus avoiding the gastrointestinal disturbances often seen with intravenous HN_2 therapy, and making it useful in treating ambulatory patients. The toxic effects of triethylene melamine, consisting of leucopenia, thrombocytopenia and anemia, are similar to those seen with HN_2. Triethylene melamine must be used very cautiously in lymphatic leukemia, employing a small test dose initially with subsequent frequent white cell and platelet determinations. The oral dose must therefore be very carefully controlled in order to avoid undue bone marrow depression.

QUANTITATIVE EXFOLIATIVE CYTOLOGY: DIFFERENTIAL COUNTING OF URINE SEDIMENT AND CERVICAL SMEARS FROM PREGNANT AND NON-PREGNANT WOMEN STAINED FOR GLYCOGEN. *Alvan G. Foraker, M.D., Darnell L. Brawner, M.D. and John D. Keye, Jr., M.D.* (From the Department of Pathology, Emory University School of Medicine and Grady Memorial Hospital, Atlanta, Ga.)

A method has been developed by which certain biologic changes are evaluated quantitatively through combining the methods of histochemistry and exfoliative cytology. This method has been applied to changes in the glycogen content of epithelial cells from the cervix and in urine sediment in pregnancy.

Cervical smears from eighteen pregnant and fifteen non-pregnant women were stained for glycogen by the periodic acid Schiff's method. Cells taking or failing to take the periodic acid stain were counted. The percentage of glycogen-containing cells was obtained through comparison between undigested and saliva digested smears. Smears from pregnant women showed a mean of 42.0 ± 20.7 per cent of glycogen-containing epithelial cells. Smears from non-

pregnant women showed a mean of 22.6 ± 15.8 per cent of glycogen-containing cells. In pregnant women 79.6 ± 28.7 per cent of the positively staining cells owed their staining reaction to glycogen. In non-pregnant women 38.9 ± 24.5 per cent of the positively staining cells owed their staining reaction to glycogen. These computations differentiated the pregnant and non-pregnant women with an accuracy of from 77.8 to 93.3 per cent.

Differential counts of urine sediment smears stained for glycogen from thirty pregnant and twenty-four non-pregnant women showed almost exactly equal mean percentages (47.80 ± 14.78 and 47.65 ± 13.09 per cent, respectively) of glycogen-containing epithelial cells.

ASPIRIN (ACETYLSALICYLIC ACID) INTOXICATION, A PROPOSED NEW METHOD OF TREATMENT. *Paul D. Doolan, M.D., William P. Walsh, M.D., Laurence H. Kyle, M.D. and Henry Wishinsky, M.S.* (From the Department of Medicine, Georgetown University School of Medicine, Washington, D.C.)

Fatalities resulting from aspirin intoxication are rare. When sufficient amounts are ingested, the drug is an effective suicidal agent because it causes pathologic lesions of an irreversible nature in the central nervous system. In addition, treatment in the absence of a specific antidote depends upon rapid removal of the drug from the body.

The degree and rate of removal of salicylate in two patients submitted to hemodialysis were compared with the excretion of salicylate by two normal subjects. The results, expressed as either clearance or total excretion, demonstrate that aspirin is removed more rapidly by the artificial kidney than by the normal kidney. Application of hemodialysis to patients with severe aspirin poisoning would consequently offer a logical approach to therapy. One moribund patient with severe aspirin intoxication, who had a marked respiratory alkalosis, was treated with the artificial kidney. Only one hour of hemodialysis was accomplished, but in that time 1,300 mg. of salicylate were recovered.

CEREBRAL FUNCTIONS IN ACUTE AND CHRONIC CEREBRAL VASCULAR DISEASE: EFFECTS OF INHALATION OF HIGH CONCENTRATIONS OF OXYGEN. *Albert Heyman, M.D., John L. Patterson, Jr., M.D. and T. Whatley Duke, M.D., Atlanta, Ga.*

Cerebral circulation and metabolism were studied with the nitrous oxide technic in twenty-seven patients with hypertensive and arteriosclerotic cerebral vascular disease. The cerebral blood flow (CBF) and cerebral metabolism ($CMRO_2$) were diminished to a mean value of 40 cc. and 2.4 cc./100 gm. brain/min., respectively, reductions of 20 per cent from normal control values. There was little difference noted between the mean CBF and $CMRO_2$ values in patients with recent or long-standing cerebral vascular accidents, senile dementia or hypertensive encephalopathy.

Cerebral blood flow determinations were repeated in ten of the patients with cerebral vascular disease during inhalation of 85 to 100 per cent oxygen. The mean CBF showed a slight fall while the mean $CMRO_2$ remained unchanged. Oxygen inhalation produced similar results in normal individuals. One patient with previous convulsive seizures developed repeated convulsive attacks during oxygen inhalation. Another individual showed a moderate fall in CBF and a striking reduction in $CMRO_2$ (3.6 to 2.7 cc.) during oxygen inhalation, and had a second stroke immediately thereafter. These studies indicate that oxygen in high concentration does not improve cerebral function in patients with cerebral vascular disease and may, in some instances, produce undesirable effects.

USE OF CONTINUOUS OXIMETRIC TECHNIC IN THE STUDY OF THE CEREBRAL CIRCULATION. *John L. Patterson, Jr., M.D., John L. Cannon, M.D. and James V. Warren, M.D.* (From the Departments of Physiology and Medicine, Emory University School of Medicine, Atlanta, Ga.)

Under conditions in which the oxygen uptake of the brain remains relatively constant, changes in the cerebral arteriovenous oxygen difference will inversely reflect alterations in blood flow.

Continuous measurement of changes in cerebral arteriovenous oxygen difference was made with two double-scale absolute-reading oximeters. Arterial and jugular venous blood was withdrawn at constant rate through the oximeter cuvettes. Heparin (25 to 30 mg.), administered intravenously, permitted fifteen to twenty minutes of blood sampling before clotting supervened.

Hyperventilation of moderate degree in ten subjects produced a rapid increase in cerebral A-V oxygen difference which began within twenty to forty-five seconds. Continuation of the hyperventilation for three minutes was associated with further increase in the oxygen

difference to a peak value averaging approximately 20 per cent greater than that in the control period. Following cessation of hyperventilation the A-V oxygen difference remained above the control level for two to five minutes and in most cases then fell to, or below, the control value.

Similar studies were done before and during head-up tilting in six subjects. Tilt to 25 degrees produced little change in A-V oxygen difference. Tilt to 45 to 70 degrees was followed within one minute by increase in the oxygen difference, which reached a maximum value 85 per cent above the control level.

Since this technic provides continuous information, it permits study of the time relationships of events in the cerebral circulation not possible with the nitrous oxide method.

SPLANCHNIC REMOVAL OF BACTERIA FROM THE BLOOD STREAM OF LEUKOPENIC RABBITS. *Grace P. Kerby, M.D. and Samuel P. Martin, M.D.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

The efficiency of the splanchnic removal of bacteria from the circulating blood has been studied in rabbits subjected to profound damage of the blood-forming tissues by the use of benzene and mechlorethamine hydrochloride. No impairment of efficiency of the splanchnic removal mechanism could be demonstrated in these animals by a method of constant intravenous infusion of M. aureus combined with the technic of hepatic venous catheterization. The peripheral white blood cell counts ranged from 40 to 400 per cu. mm. at the time the bacteremia was induced. The phagocytic activity of the Kupffer cells of the liver and of the macrophages of the spleen was demonstrated histologically by the terminal administration of thorotrast or India ink.

The importance of the peripheral white blood cell in the establishment and clearing of the bacteremias appears to be in its phagocytic activities at the local source of the bacteremia rather than in any quantitatively significant phagocytosis of organisms circulating in the blood stream. The present studies suggest that attention should be directed in the leukopenic state more especially toward the identification and eradication of the local source of organisms.

QUANTITATIVE STUDY OF THE DURATION AND DEGREE OF THOROTRAST INTERFERENCE WITH THE REMOVAL OF BACTERIA FROM THE SPLANCHNIC CIRCULATING BLOOD OF THE INTACT RABBIT. *Samuel P. Martin, M.D. and Grace P. Kerby.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

The present study explores quantitatively the splanchnic mechanism for the removal of Micrococcus aureus from the blood stream at periods ranging from one hour to seventeen days after the intravenous injection of thorotrast into the rabbit. The duration and degree of thorotrast effect on the removal of the bacteria has been determined by a method of continuous intravenous infusion of Micrococcus aureus combined with a technic of venous catheterization for obtaining repeated samples of blood for culture. The samples were obtained by means of repeated cardiac punctures or inferior vena cava catheterization and simultaneously by hepatic venous catheterization. The resultant data show a significant and steady decrease in the per cent splanchnic removal rate of M. aureus from the first hour to nineteen to twenty-four hours after thorotrast, with a gradual return to control levels eight days after thorotrast. The rate is maximally decreased from control levels of 62 per cent $\pm$ 20 (S.D.) to 19 per cent $\pm$ 4 (S.D.) nineteen to twenty-four hours after thorotrast. The mechanism by which thorotrast interferes with the efficiency of bacterial removal from the blood stream remains obscure.

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE WESTERN SECTIONAL MEETING IN SEATTLE, WASHINGTON, JANUARY 25, 1951

RESPIRATION OF HUMAN CEREBRAL CORTEX SLICES AS AFFECTED BY PATHOLOGIC STATES, ELECTROSHOCK THERAPY AND ELECTROENCEPHALOGRAPHIC FINDINGS. *H. W. Elliott, M.D., V. C. Sutherland, M.D., E. B. Boldrey, M.D. and J. E. Adams, M.D.* (From the Departments of Pharmacology and Experimental Therapeutics, Neurosurgery and the Langley Porter Clinic, University of California School of Medicine, San Francisco, Calif.)

The oxygen uptake of human cerebral cortex slices from patients undergoing surgery for neuropathologic or psychiatric reasons has been measured by the direct method of Warburg. The findings have been correlated with histopathology, electroshock therapy and electroencephalographic changes.

In non-psychiatric patients the oxygen uptake of degenerate cortex is significantly reduced below the value for cortex which showed no histopathology. The reduction is even more marked when there is evidence of neoplastic infiltration. The oxygen uptake of tissue obtained from lobotomy operations when classified according to the number of electroshock treatments received showed the greatest decrease below control values following twenty-five to fifty shock treatments. If several treatments had been given shortly before lobotomy, the values approached those of the control. This effect was not apparent in the presence of glucose substrate. There was no correlation between oxygen uptake and electroencephalographic findings.

REMISSION IN IDIOPATHIC THROMBOCYTOPENIC PURPURA DURING THE ADMINISTRATION OF ACTH. *R. S. Evans, M.D.* (From Stanford University School of Medicine, San Francisco, Calif.)

The administration of ACTH to a patient with chronic unremitting idiopathic thrombocytopenic purpura was followed by a return of capillary fragility to normal, a reduction in prolonged bleeding time to normal and a disappearance of purpura. The highest platelet count during the previous two years was 30,000 per cm. During ACTH administration the count rose to 135,000 per cm. The clinical improvement continued approximately two months after cessation of ACTH administration. The remission observed is compatible with the postulate that idiopathic thrombocytopenic purpura is due to an abnormality of plasma proteins similar to that seen in acquired hemolytic anemia and with reports of response of the latter disease to ACTH administration. A quantitative reduction in the abnormal platelet agglutinating factor present in the patient's serum could not be demonstrated during ACTH administration.

THE UPTAKE OF P^{32} IN THE DNA FRACTION OF LYMPHOCYTES AND GRANULOCYTES FROM PATIENTS WITH LEUKEMIA. *Edwin E. Osgood, M.D., Harold Tivey, M.D., Kenneth B. Davison and Arthur J. Seaman, M.D.* (From the University of Oregon School of Medicine, Portland, Ore.)

Radioactive phosphorus (P^{32}) uptake in the desoxyribose nucleic acid (DNA) fraction of leukocytes has been measured *in vitro* and *in vivo* in cells from patients with leukemia. The results show significantly less uptake, *in vitro* and *in vivo*, in cells from patients with lymphocytic leukemia than in patients with granulocytic leukemia of equal clinical chronicity. Uptake rates of DNA P^{32} in culture demonstrate new cell formation in patients with chronic granulocytic or acute lymphocytic leukemia, but not in cells from patients with chronic lymphocytic leukemia during the seven-day time interval studied.

ADRENALIN TEST IN HYPERSPLENISM. *Arthur A. Marlow, M.D. and Robert A. Kallsen, M.D.* (From The Scripps Metabolic Clinic, La Jolla, Calif.)

The hypotheses of "hormonal inhibition" and "splenic sequestration" have been used to explain the etiology of the cytopenic syndromes which are called "hypersplenism." The response of circulating blood cells to adrenalin has been described as being of diagnostic value in hypersplenism.

The circulating leukocyte and erythrocyte changes after adrenalin in cases of hypersplenism were compared with those found in normal and splenectomized individuals. The initial leukocyte counts were lowest in hypersplenism and highest in splenectomized patients but the net gain in leukocytes was of the same magnitude in all three groups. Granulocyte and thrombocyte responses followed a pattern similar to the total leukocyte change. Erythrocyte changes in some instances of hemolytic anemia showed a greater net gain than that found in normal or splenectomized patients.

HEPATIC ARTERIOGRAPHY AND THE EFFECT OF INTRA-ARTERIAL CHEMOTHERAPEUTIC AGENTS ON METASTATIC NEOPLASMS OF THE LIVER. *Howard R. Bierman, M.D., Ralph L. Byron, Jr., M.D. and Keith H. Kelly, M.D.* (From the Laboratory of Experimental Oncology, National Cancer Institute, National Institutes of Health, Public Health Service and the University of California School of Medicine, San Francisco, Calif.)

Seventy-five arteriograms of the liver have been obtained in thirty-six patients by intra-arterial catheterization. Increased vascular patterns with irregular branching and bizarre formations have been found to be characteristic of neoplastic involvement.

Since the blood supply to such hepatic metastases had been previously shown to be almost exclusively from the hepatic artery both by dye perfusion and by arteriography *in vivo*, methyl bis (beta chloroethyl) amine was administered intra-arterially in doses of 0.6 to 2.4 mg./kg. body weight, or triethylene melamine was given arterially in doses of 0.1 to 0.3 mg./kg. Forty such administrations have been given to thirty-six patients with various far advanced neoplastic diseases. No untoward changes in liver function tests have been detected. Decrease in palpable nodules of the liver was commonly observed following the nitrogen mustard. Improvement was observed in 60 per cent. Fifteen per cent of the patients survive at present for periods of four to twelve months.

EXPERIMENTAL PRODUCTION OF NODAL RHYTHMS IN HUMAN SUBJECTS. *Merrill C. Daines, M.D. and Hans H. Hecht, M.D.* (From the Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.)

The observations by Wilson (1915) that the atrioventricular node of the normal human heart is released from the effects of vagal stimulation before the sinus node, has led to the experimental production of abnormal auricular rhythms in normal young adults. Twenty-five subjects (aged twenty-two to thirty-four) received 1 mg. of neosynephrine hydrochloride by vein. The peripheral effects of this sympathomimetic compound outweigh its cardiac action and therefore an abrupt rise in peripheral resistance without cardiac acceleration occurs immediately upon the injection. This is followed promptly by vagal reflex suppression of sinus activity with pronounced bradycardia and is characterized by the appearance of abnormal, slow, supraventricular rhythms, often preceded or followed by periods of excessive PR prolongation and auricular standstill. Various types of "coronary sinus" and atrioventricular nodal rhythms occurred lasting up to two minutes in twenty-three of the twenty-five subjects. Shifting of the abnormal pacemaker within the node occurred seven times.

The chain of events can be blocked by dibenamine and by atropine and can be interrupted by amyl nitrite. The ventricular complexes of the nodal beats showed almost invariably some alteration in form, suggesting that vagal stimulation may influence impulse conduction over ventricular tissues. The technic is useful for a number of clinical and physiologic problems.

CLINICAL TRIAL OF DIPHENHYDRAMINE IN AURICULAR FIBRILLATION. *H. Lenox H. Dick, M.D. and Elton L. McCawley, M.D.* (From the Department of Pharmacology, University of Oregon Medical School, Portland, Ore.)

Studies show that diphenhydramine resembles quinidine in its ability to prolong the refractory period of the isolated auricle, to elevate the threshold of the myocardium to electrical stimulation, to exhibit an antivagal action and to convert induced auricular fibrillation and flutter in dogs or rabbits to normal rhythm. A mild atropine-like action and a synergistic action with epinephrine also has been observed. Toxicity studies in dogs indicate no serious untoward cardiac effects. The antifibrillatory action of diphenhydramine was compared with quinidine in twelve patients with auricular fibrillation. Diphenhydramine was given intravenously with continuous recording of the electrocardiogram. With diphenhydramine alone there were six conversions to normal sinus rhythm which could be maintained by oral diphenhydramine. Conversion failed in two

cases after intravenous diphenhydramine but large oral doses of quinidine sulfate were effective. In the remaining four patients both diphenhydramine and quinidine sulfate failed to convert the fibrillation to normal rhythm. Side effects noted were: transitory drowsiness, vertigo, haziness of vision and frontal headaches. Some rise in both systolic and diastolic (10 to 20 mm. Hg) pressures was observed. In one patient transitory visual hallucinations were noted following intravenous diphenhydramine while another showed some memory loss for recent events while on an oral maintenance dose.

RENAL EXCRETION OF DIGITOXIN AS AN INDICATOR OF (1) ADEQUATE AND (2) EXCESSIVE DIGITALIZATION. *Meyer Friedman, M. D., Rene Bine, Jr., M.D. and Sanford O. Byers, Ph.D.* (From The Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.)

The renal excretion of digitoxin was determined in fourteen chronic cardiac patients who had been and were continued in an adequate state of digitalization. The renal excretion of the same glycoside was determined nine times in seven subjects at the time they exhibited signs and symptoms of digitoxin intoxication. Assay of digitoxin in urine samples was accomplished by previously described methods employing the embryonic duck heart as the indicator of digitoxin concentration.

The experimental results indicated that an adequate state of chronic digitalization was characterized by a daily excretion of digitoxin of not less than 21 nor more than 56 micrograms per day. These values were found to be approximately the same as that found in normal young subjects theoretically digitalized. Intoxication with digitoxin, on the other hand, was indicated by a renal excretion of digitoxin varying from 72 to 132 micrograms per day.

NATURAL HISTORY AND COURSE OF MALIGNANT HYPERTENSION. *Mary F. Schottstaedt, M.D. and Maurice Sokolow, M.D.* (From the University of California School of Medicine, San Francisco, Calif.)

As part of a long-range study of the natural history of hypertension a survey was made of all cases of malignant hypertension seen in the past ten years at the University of California Hospital. Papilledema in the presence of severe hypertension was accepted as the criterion for diagnosis. One hundred four cases were included; follow-up information was obtained in all. The average survival after the discovery of papilledema was thirteen months in patients with good renal function and four months in those with impaired renal function. In ten well documented cases renal impairment developed in an average of 4.4 months. Autopsies, performed in thirty-one cases, revealed the basic renal lesion to be nephrosclerosis in twelve, pyelonephritis in twelve and glomerulonephritis in seven.

Only patients in whom papilledema disappeared survived more than thirty months. With the exception of one patient with glomerulonephritis none in whom papilledema disappeared died of renal insufficiency. This is in contrast to the usual course in untreated patients. Disappearance of papilledema implies a decrease in tempo of malignant hypertension and reversal to benign hypertension. Provided vascular damage is not too extensive, an increased survival rate may be expected. Early and vigorous treatment is essential in malignant hypertension (1) before renal function is impaired and (2) before irreparable damage to cerebral and cardiac vessels has occurred.

TREATMENT OF CHRONIC SHIGELLA INFECTIONS IN CHILDREN WITH ORAL POLYMYXIN. *D. Lieberman, M.D. and E. Jawetz, M.D.* (From the Divisions of Psychiatry, Bacteriology and Pediatrics, University of California, School of Medicine, San Francisco, Calif.)

The newer antibiotics have proven successful in controlling acute bacillary dysentery but are much less effective in chronic shigella infections in children. A single course of a sulfonamide, chloramphenicol or aureomycin cured 93 per cent of 116 patients with acute shigellosis but only 63 per cent of 78 chronic relapsing patients or carriers.

Polymyxin is a very active drug *in vitro* against shigella, 0.05 microgram/ml. or less inhibiting most strains completely. Polymyxin is too toxic for routine parenteral administration but is not significantly absorbed from the intestinal lumen, producing no irritation or toxic effects after oral administration. Consequently, polymyxin was employed in chronic shigella infections of children that had previously failed to be cured.

Twenty-three chronic relapsing patients or carriers were placed into isolation wards after Shigella flexneri had been isolated from their stools twice in succession, and were given 15 to 20 mg./kg./day polymyxin E or B by mouth for ten days. Cultures were taken during therapy

and for eight weeks thereafter. Careful laboratory studies and clinical observation checked on possible absorption and toxicity of the drug.

Twenty children (87 per cent) were unequivocally cured whereas three carriers had bacteriologic relapses three to six weeks after termination of treatment. No evidence of absorption of the drug or toxicity was encountered. Polymyxin appears to be a highly effective and safe drug for the oral treatment of shigella infection.

USE OF AUREOMYCIN IN THE TREATMENT OF CONGENITAL FIBROCYSTIC DISEASE. *Henry B. Bruyn, M.D.* (From the Division of Pediatrics of the University of California Medical School, and the Infectious Disease Laboratory of the San Francisco City and County Hospital, San Francisco, Calif.)

The major problem in the treatment of children with fibrocystic disease of the lungs and pancreas has been to control the repeated pulmonary infections which remain the principal cause of death. The present study involves the use of aureomycin over a period ranging from two to twenty months in thirty cases of proved fibrocystic disease with pulmonary involvement.

The children were placed on a dosage of 125 mg. of aureomycin twice a day. Weight gain and appetite were improved during aureomycin therapy in most instances. In ten children in whom aureomycin therapy was instituted within six months of the onset of symptoms of this disease the course approximated that of a normal child. Five children died during therapy, two of these deaths attributable to fibrocystic disease alone. Eighteen of the thirty children had a good result, with marked diminution or complete disappearance of the cough characteristic of this disease. An additional nine patients had slight improvement and were better than on any other form of therapy.

EFFECTIVENESS OF A NEW COMPOUND, BENEMID,® IN ELEVATING SERUM PENICILLIN CONCENTRATIONS. *James M. Burnell, M.D. and William M. M. Kirby, M.D.* (From the University of Washington School of Medicine, Seattle, Wash.)

The effect of the oral administration of 0.5 gm. of benemid® every six hours on serum penicillin levels was measured in seventy-four adult patients. In fifty-one patients treated with procaine penicillin there was enhancement of penicillin levels following benemid® in 81 per cent of the instances, with an average fold increase of 2.87. In twenty-three patients treated with crystalline penicillin the levels were higher in 96 per cent of the cases, with an average fold increase of 5.10. Increases in penicillin levels of three- to fivefold following benemid® should make the therapy of certain penicillin-resistant infections both less expensive and mechanically less difficult.

USE OF HYALURONIDASE IN THE INTRAMUSCULAR ADMINISTRATION OF AUREOMYCIN. *Benjamin Sugar, M.D., Henry B. Bruyn, M.D., Mirra Scaparone, A.B. and Henry D. Brainerd, M.D.* (From Stanford University School of Medicine and University of California School of Medicine, San Francisco, Calif.)

Aureomycin was given to seventeen individuals intramuscularly in doses of 50 to 200 mg., dissolved in 5 ml. of a mixture of equal parts of Sorenson's phosphate buffer and 1 per cent procaine. Only three of these individuals showed measurable amounts of aureomycin in the serum within three hours of injection. The maximum level observed was 1.2 micrograms per ml. of serum fifteen minutes after the tenth such consecutive injection of 100 mg. in one patient.

Aureomycin was administered intramuscularly to eight individuals in doses of 250 mg. dissolved in a sodium glycinate buffer solution. After a four-hour period serum concentrations of 0.15 to 0.6 micrograms per ml. were observed in six of these individuals. After an interval of two days six of these same individuals received the same dose of aureomycin intramuscularly in combination with 250 viscosity units of hyaluronidase. Serum concentrations of 0.15 to 10.0 micrograms per ml. were observed four hours following injection in all of these subjects. Significant blood levels appeared at two hours and persisted at least as long as twelve hours in all instances when hyaluronidase was added.

The intramuscular injection of aureomycin was painful in all instances and the addition of procaine did not diminish this complaint.

SERUM CHOLINESTERASE IN HEPATIC DISEASE. *Kenneth Fremont-Smith, M.D. and Wade Volwiler, M.D.* (From the University of Washington School of Medicine, Seattle, Wash.)

Non-specific serum cholinesterase is an alpha-globulin without known function. From animal experiments it has been proposed that the enzyme is elaborated by the liver. Clinical studies by others have shown that a low serum

cholinesterase level is found predominantly in patients with disease of the hepatic parenchyma. It has been suggested that serial cholinesterase determinations might provide a better prognostic index in such diseases as infectious hepatitis and decompensated cirrhosis than the liver function tests in current use.

We have confirmed the finding that abnormally low serum cholinesterase activity is found in patients with either diffuse hepatic disease or severe malnutrition. Serial determinations in cirrhotic patients have shown that the enzyme level, while paralleling the serum albumin concentration, may be a more sensitive prognostic indicator in certain cases than the conventional tests for liver function. A direct relationship between serum cholinesterase activity and serum albumin concentration in both normal and pathologic sera has also been demonstrated.

AN EXPERIMENTAL STUDY OF THE EFFECTS OF BANTHINE® UPON GASTRIC SECRETION AND PEPTIC ULCERATION. *Lester R. Sauvage, M.D. and Henry N. Harkins, M.D.* (From the University of Washington School of Medicine, Seattle, Wash.)

The ideal of ulcer therapy is a medical cure of a permanent nature. The ulcers of the gastric rumen in starved rats subjected to the Shay procedure of pyloric ligation are prevented by vagotomy, banthine® and atropine. The gastric free hydrochloric acid secretory response to histamine stimulation is markedly depressed by both banthine® and atropine. The peptic ulceration of the jejunum adjacent to the gastrojejunostomy in the Mann-Williamson dog is prevented in most cases by banthine.® These results do not categorize banthine® as the best or preferred method of therapy of peptic ulceration in man but they would seem to indicate its probable value.

INSULIN TOLERANCE TESTS IN PATIENTS RECEIVING LARGE DOSES OF EXOGENOUS INSULIN. *Gerald T. Perkoff, M.D. and Frank H. Tyler, M.D.* (From the University of Utah School of Medicine, Salt Lake City, Utah.)

In 1938 Fraser et al. reported that the hypoglycemia caused by the administration of small intravenous doses of crystalline insulin to patients with islet cell adenomas is not followed by the hyperglycemia which occurs in normal individuals, a phenomenon referred to as hypoglycemia unresponsiveness. Although such an intravenous insulin tolerance test has been used extensively in the study of certain other disorders, e.g., adrenal insufficiency, its validity as a diagnostic tool in islet cell adenoma has been questioned.

Intravenous insulin tolerance tests have been performed in patients receiving insulin shock therapy for psychoses. Each patient had received excessive doses of insulin five times weekly for several weeks. The results of the insulin tolerance tests in these patients were within the limits of normal. The blood sugar fell to hypoglycemic levels at thirty minutes and returned to control levels or above at one hour. Thus it would appear that their insulin sensitivity remained the same in spite of the repeated administration of large doses of insulin.

EVALUATION OF THE METABOLIC DEFECT IN "IDIOPATHIC HYPOPROTEINEMIA"; ITS MODIFICATION BY VARIOUS THERAPEUTIC AGENTS; AS STUDIED WITH THE AID OF S-35 LABELED METHIONINE. *Sheldon Margen, M.D., Laurance W. Kinsell, M.D., Judith Lange, A.B., Harold Tarver, Ph.D. and George Michaels, Ph.D.* (From the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.)

Over a three-year period numerous studies have been carried out on a forty-two year old male patient suffering from severe hypoproteinemia (hypoalbuminemia) of unknown origin.

Normal individuals have a predictable pattern of incorporation of S-35 into plasma protein and of excretion of S-35 in the urine. Four studies have been carried out in this patient. Two control studies were performed almost exactly one year apart, a third study on testosterone propionate, and a fourth during and following the administration of serum albumin in sufficient quantities to bring the plasma levels to normal. The rate of incorporation of S-35 into plasma protein and its rate of disappearance greatly exceeded that of the normal. Testosterone propionate administration did not significantly alter this pattern. During the albumin study the pattern of S-35 incorporation into plasma protein approached that of the normal. The rate of disappearance continued at a rate in excess of the normal.

Significant deviations from the normal were observed in the pattern of urinary inorganic sulfate excretion. These findings together with the plasma protein studies are compatible with the concept of increased catabolism as the fundamental metabolic defect in this syndrome.

The urinary excretion of inorganic and

organic sulfur were modified during the administration of testosterone and of plasma albumin.

METHYLANDROSTENEDIOL: ITS PRESENT CLINICAL STATUS. *Gilbert S. Gordon, M.D.* (From the University of California School of Medicine, San Francisco, Calif.)

The clinical use of protein-anabolic steroids for stimulation of tissue formation has been limited by the fact that these compounds are also potent androgens. It has been hoped that by use of an appropriate assay procedure suitable steroids might be recognized which possess anabolic properties similar to those of testosterone but have little or no androgenic activity. During the screening of a number of compounds it was found that methylandrostenediol is a potent protein-anabolic steroid with little genital activity. Balance studies in female human subjects have confirmed the anabolic efficacy of this compound. The compound has proved effective for weight gain, increase in height and stimulation of bone matrix formation. Of greatest interest is the dearth of other effects which might be anticipated from administration of steroids (masculinization, inhibition of menses, untoward emotional responses).

Present early evaluation indicates that methylandrostenediol is a promising experimental agent with metabolic actions similar to those of methyltestosterone but, in ordinary doses (20 to 40 mg. per day sublingually), little or no genital activity.

SIMULTANEOUS MEASUREMENT OF SEVERAL COMPONENTS OF PLASMA AND OF INTERSTITIAL FLUID. *W. W. Hurst, M.D., F. R. Schemm, M.D. and J. A. Layne, M.D.* (From the Great Falls Clinic, Great Falls, Mont.)

Tissue fluids were obtained free of blood in the manner described by Burch in thirteen patients with cardiac edema.

Sodium (twelve studies): The sodium levels in the tissue fluid were lower than in the blood plasma in ten instances; average difference 3.0 mEq./L. (1 to 7 mEq./L.). In two instances the tissue fluid sodium excess was 2 and 5 mEq. (In two instances potassium levels were determined and were identical in tissue and plasma.)

Chloride (eleven studies): Tissue fluid values were higher than in the plasma in all instances; average difference 9.3 mEq./L. (4 to 14 mEq./L.).

Carbon dioxide combining power (nine studies): Tissue fluid values were higher than plasma values in all instances. The average difference was 13.7 vol. per cent (1.9 to 23.2 vol. per cent).

Protein (twelve studies): The average values for plasma were total protein 6.2 gm. per cent, albumin 3.7 gm. per cent and globulin 2.5 gm. per cent (A/G ratio 1.5). Average values for tissue fluid were total protein 0.63 gm. per cent, albumin 0.48 gm. per cent and globulin 0.15 gm. per cent (A/G ratio 3.2).

Specific gravity (twelve studies): Average values were plasma 1.0265 and tissue fluid 1.0092.

Urea (seven studies): In six the tissue fluid levels were higher than in the plasma (one identical). Average difference was 6.6 mg. per cent (0 to 14 mg. per cent).

Non-protein nitrogen (eight studies): In six tissue fluid levels were lower than plasma levels (two identical). Average difference was 8.2 mg. per cent (0 to 16 mg. per cent).

Cholesterol (seven studies): Tissue fluid values were all less than 25 mg. per cent. Average plasma values were 177 mg. per cent (136 to 230 mg. per cent).

Calculation indicates that the greater values for chloride and bicarbonate in the tissue fluid compensate nicely for the lower number of cation charges of the tissue fluid protein. Further studies are in progress.

IRON STORES IN MAN. *Alexander R. Stevens, Jr., M.D. and Clement A. Finch, M.D.* (From the University of Washington School of Medicine, Seattle, Wash.)

Dietary iron absorption is limited to a few milligrams per day even in the severely iron-deficient individual. This is sufficient to replace a loss of 500 ml. of blood over a period of about three months. The chief defense against anemia of blood loss is a store of available iron within the body. This available iron store has been measured in adult male subjects by removal of 500 ml. of blood weekly for seven weeks. Amount from stores was represented by the total iron removed by bleeding minus red cell deficit. Approximately 1,200 to 1,500 ml. of available iron were found in normal subjects. In subjects who had no anemia but had previously donated blood repeatedly there was marked reduction in available iron stores. In patients with hemochromatosis there were unlimited stores. Intravenous iron (saccharated iron) provided a store of iron quantitatively available for hematopoiesis.

Case Reports

Periarteritis Nodosa*

Report of a Case Treated with ACTH and Cortisone

WILLIAM L. MUNDY, M.D., WILLIAM G. WALKER, JR., M.D.,
HYLAN A. BICKERMAN, M.D. *and* GUSTAV J. BECK, M.D.
New York, New York

PERIARTERITIS nodosa cannot at present be defined other than by a description of its pathologic morphology. The only hypothesis of etiology based on a significant number of facts is that of Rich and co-workers[22–26] who have observed that acute lesions of serum sickness and drug sensitivity of antigenic type in human beings, and lesions in a number of stages of advancement of serum sickness in rabbits, are morphologically similar to the lesions of human cases of periarteritis nodosa. Rich believes that an antigen-antibody reaction is a possible basic factor in the pathogenesis of periarteritis nodosa. These observations have been corroborated by Hawn and Janeway[11] who have, further, roughly correlated the active phase of arterial lesions in rabbits suffering from serum sickness with the duration of detectability of circulating antigen and of absence of antibody. Correlations have been made between the clinical course and changes in level of circulating antigen and antibody in human cases of serum sickness but no pathologic studies have been performed in these instances.[18]

A rational approach to treatment in terms of mechanisms peculiar to periarteritis nodosa is as yet impossible. The use of pituitary adrenocorticotrophic hormone and cortisone was suggested by the fact that periarteritis nodosa shares a common site of pathologic change—the extracellular connective tissue or "collagen system"[14,16]—with rheumatoid arthritis. It is to be emphasized[14,15] that the fact of such a common site implies nothing about etiologic relation among "collagen diseases."

Ragan and co-workers[7,20,21] have shown a delay in the proliferation of connective tissue elements in the repair of mechanically produced wounds in rabbits and human beings during administration of ACTH or cortisone. Ragan postulates that the action of these drugs perhaps takes place at the level of a key precursor of all fibrous tissue elements. Howes[13] has suggested that the primary effect is on vascular tissue.

At least part of the action of cortisone is probably direct since local application of amounts too small to exert a measurable systemic effect can inhibit granulation tissue in rabbits.[19] Cortisone is also effective when used locally in certain eye diseases.[10,35]

The present report continues the documentation of the effects of ACTH and cortisone in periarteritis nodosa. The limited data in the literature[6,17,27,30,32,33] justify the presentation of a single case.

CASE REPORT

L. Y., a forty-nine year old, Polish-born, white male, was transferred to the Columbia University Research Division in Goldwater Memorial Hospital on June 15, 1949, from New York Hospital. He was a civil engineer, widely travelled. His history prior to 1939 was not remarkable. In that year he suffered a stab wound involving the myocardium. Resection of the anterior portions of the fifth, sixth and seventh ribs was performed and a laceration of the left ventricle was repaired. He was asymptomatic until approximately February, 1946, when he was bothered with a hacking, nonproductive cough. The cough was resistant to usual medications and he entered Roosevelt Hospital in May, 1946. X-ray examination of the chest revealed a shadow in the left lower lung field. Bronchoscopy was negative for any intrabronchial growth and no evidence of a

* From the Columbia Research Service, Goldwater Memorial Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

primary focus for a tumor could be found. In June, 1946, a gauze sponge was removed from the region of the left lower lobe, necessitating a partial lobectomy. He made an uneventful recovery.

About one month postoperatively he again experienced a severe, non-productive cough, mostly at night, accompanied by wheezing and severe dyspnea. He also experienced some dyspnea on exertion. He was readmitted to Roosevelt Hospital where a diagnosis of allergic bronchial asthma was established. A chest x-ray revealed considerable pleural change at the operative site of the mid-left lung field and at the left lung base. An electrocardiogram was normal. Skin test reaction showed allergy to house dust, ragweed, aspergillus, monilia and hormodendron. These molds and ragweed were thought to account for the onset of symptoms. Because it was believed that the patient might have some bronchopulmonary infection, he was given penicillin for a ten-day period, as well as anti-asthmatic medications. After two weeks' hospitalization the patient had improved considerably and the lungs were clear.

One month following discharge he developed a pleuritic-type pain and a left-sided pleural effusion was visible by x-ray. The characteristics of the fluid are not known. The pleurisy subsided within two months but his asthmatic condition was quite disabling.

He entered New York Hospital in March, 1947, where the diagnoses of bronchial asthma, chronic pansinusitis and questionable bronchiectasis were made. A bilateral Caldwell-Luc procedure and polypectomy offered some relief. He returned home in April, 1947, and remained there, restricted to rather limited activity for nearly two years. The frequency of his asthmatic attacks remained the same. Because his disability underwent no regression he decided to change his environment.

In March, 1949, he arranged for an automobile trip to Florida. The day before leaving he developed a slight cold and the first day of the trip left him exceedingly fatigued. His asthma, however, was less severe than it had been for several weeks. Three days after the onset of the cold he noted swelling of both feet and a 20 degree flexion deformity of the third and fourth fingers of the right hand. He had no fever at that time and suffered no pain. On the following day his temperature was 101°F. and he gave himself an injection of penicillin. The next day the temperature rose to 103°F. and a physician was called. The swelling of the feet remained as did the flexion of the fingers. He was given penicillin for two more days without effect. Aching pain in the hands and feet supervened and he was admitted to a hospital.

Laboratory findings in Florida included a red blood cell count of 4,520,000, hemoglobin 76 per cent, white blood cell count 18,900, with 69 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 2 per cent monocytes and 10 per cent eosinophils. Erythrocyte sedimentation rate was 23 mm. in one hour and the urine examination was negative. A blood culture was negative and no malarial parasites were seen. His sputum revealed no acid-fast bacilli. Agglutination tests for typhoid O and H, paratyphoid A and B, Brucella abortus and proteus OX19 were negative. A Kahn test was negative. A fasting blood sugar of 119 mg. per cent and a non-protein nitrogen of 37 mg. per cent were recorded. The electrocardiogram was considered normal. No report of his chest x-ray is available.

Following a blood transfusion he suffered a severe shaking chill; his temperature rose to 105°F.; a petechial rash appeared over the legs and feet and he became extremely weak. The feet swelled to three times normal size and he suffered burning pain associated with pins-and-needles sensation in the feet, legs, shoulders, arms and hands. The pain was severe enough to necessitate frequent opiates and sedation. Dihydrostreptomycin had been given for five days in an attempt to lower his temperature. This was discontinued with the onset of the chill and he was given aureomycin. After remaining at 104°F. for two days following the chill the temperature dropped precipitously to normal.

All symptoms of asthma disappeared during the acute febrile episode. The marked pain in the hands and feet continued; the rash disappeared; he remained free of asthmatic symptoms and was afebrile for the last nine days of his hospitalization. Upon arrival in New York he remained at home for ten days. The pain in his hands and feet became so disabling that any motion caused such excruciating pain that he was unable to feed himself or walk.

He was readmitted to New York Hospital on April 26, 1949, with the complaint of severe pain in the extremities, especially marked in the left hand, right forearm, both knees and both feet. It was not localized in the joints. Burning

pain associated with paresthesias was present in some degree constantly but was exaggerated by movement or palpation. Examination revealed a blood pressure of 140/95. The eyes were considered normal. There was bilateral posterior cervical and axillary adenopathy. The heart, lungs and abdomen were unremarkable. There was no costovertebral angle tenderness. Examination of the extremities revealed considerable weakness in the hands and feet accompanied by pallor and blotchy cyanosis. Tenderness was especially marked over the left hypothenar eminence, right wrist, both hands and both feet. The ulnar, popliteal and brachial arteries were tender on palpation but no nodules were felt in these areas. There was no edema. Nerve tenderness was not mentioned. Deep tendon reflexes were absent throughout.

The red blood cell count was 5 million with 15.5 gm. of hemoglobin. White blood cell count was 25,800 with 23 per cent mature polymorphonuclear leukocytes, 10 per cent lymphocytes, 1 per cent monocyte and 66 per cent eosinophils. The urine showed a specific gravity of 1.023, a trace of albumin, occasional red blood cells, 1 to 3 white blood cells, rare hyalin casts and no sugar. The blood urea nitrogen was 13 mg per cent, total protein was 6.3 gm. per cent with 3.5 gm. per cent albumin and 2.8 gm. per cent globulin. Mazzini and spinal fluid Wassermann tests were negative. Stool guaiac tests were occasionally faintly positive; stool cultures were negative. Agglutination tests for typhoid O and H, paratyphoid A and B, proteus OX19 and Shigella were negative. Trichinella precipitin test was positive in a dilution of 1:1280. Spinal fluid pressure was normal. The fluid contained one lymphocyte and total protein was 24 mg. per cent. Culture was sterile and the gold curve was 1122100000. No change was noted in his chest film from that taken in March, 1947. Electrocardiogram revealed only left electrical axis deviation. An electroencephalogram was interpreted as a pathologic record showing non-specific slow activity. Skin and muscle biopsies showed degenerative and inflammatory changes in the muscles, with collections of eosinophils, lymphocytes and plasma cells about many of the capillaries. The biopsy sections were thought to be compatible with a diagnosis of periarteritis nodosa.

The hospital course was one of gradual increase in the symptoms of peripheral neuropathy, marked by the development of numbness of the hands and feet and frequent attacks of pain and acute muscle tenderness in the extremities. There were no periods of remission. He had one week of minimal diarrhea which cleared without therapy.

He was transferred to Goldwater Memorial Hospital on June 15, 1949, with essentially the same complaints as noted above. Examination revealed a chronically ill, emaciated male, suffering pain on any motion. The blood pressure was 120/80. There was minimal cervical and axillary adenopathy. The lungs, heart and abdomen were unremarkable. Wasting of the musculature of the extremities was present, especially in their periphery, and there was notable atrophy of the thenar and hypothenar eminence and of the interosseous regions, the right greater than the left. The dorsa of the hands were board-like. Mottled cyanosis of the legs, feet and hands was present. There was marked weakness of the upper and distal lower extremities (the right greater than the left) with atrophy of the thenar and interosseus regions. There was loss of function in radial and ulnar distribution (right greater than left) and bilateral footdrop. Muscular weakness in the shoulders and arms was so marked that he was unable to change his position in bed. He had no use of his hands and could barely move his fingers. There was involvement of all modalities of sensation, especially on the right, with tenderness of the nerves, much delayed pain perception, dysesthesia and faulty localization. The cranial nerves were intact. The impression was polyneuropathy secondary to periarteritis nodosa. In view of his critical condition and the progressive course of his disease his prognosis was considered hopeless.

Laboratory examinations revealed a hemoglobin of 13 gm., an hematocrit of 44 per cent, red blood cell count of 4,500,000, white blood cell count 12,000 with 50 per cent polymorphonuclear leukocytes and a 35 per cent eosinophilia. The erythrocyte sedimentation rate (Westergren method) was 49 mm. in one hour. Urinalysis was negative. Non-protein nitrogen was 32 mg. per cent and the blood urea nitrogen 18 mg. per cent. He had a normal glucose tolerance curve and a fasting blood sugar of 73 mg. per cent. Phenolsulfonphthalein excretion was 70 per cent in two hours. Urea clearance was normal and maximum urine concentration was 1.028. Three stool guaiacs in the first three months were negative. The serum albumin was

3.6 gm. per cent, serum globulin 2.9 gm. per cent, serum total cholesterol 212 mg. per cent, cholesterol ester fraction 153 mg. per cent, alkaline phosphatase 4.2 King-Armstrong units, serum bilirubin 0.4 mg. per cent, bromsulfalein retention 1 per cent, prothrombin time (modified Quick method) 13 seconds undiluted and 43 seconds in 12½ per cent dilution, thymol turbidity 2.3 units and cephalin flocculation was negative in forty-eight hours. Mazzini and quantitative Kolmer tests were negative. Trichinella precipitin test was negative on July 5, 1949. Spinal fluid pressure was normal and the total protein was 22 mg. per cent. Colloidal gold curve was 0000000000.

Electrocardiograms again showed only left axis deviation. X-rays of the skull, spine, chest, abdomen and long bones revealed no significant abnormalities.

During the next three months the patient was treated symptomatically. Demerol and codeine were adequate for the relief of pain. Two-plus to three-plus albuminuria developed, and from 5 to 10 white blood cells and 5 to 20 red blood cells were found in serial urine examinations. White blood cell counts ranged as high as 17,300, with an eosinophilia from 20 to 52 per cent. Total eosinophile counts (phloxine-propylene glycol technic) varied from 1,360 to 7,300. The sedimentation rate was elevated to 100 mm. in one hour. The serum total cholesterol fell to 158 mg. per cent with an ester fraction of 118 mg. per cent. The blood urea nitrogen was not higher than 18 mg. per cent. On October 18, 1949, the serum albumin was 3.0 gm. per cent and the serum globulin was 3.8 gm. per cent.

Throughout September, 1949, the patient's asthmatic symptoms returned gradually, and in late October, 1949, he suffered a severe asthmatic attack. From that time on he required daily adrenalin and aminophyllin for relief of asthma. The deep and productive cough became a permanent feature of his illness.

He felt that he had had a significant decrease in his pain from July to October, 1949, and a like increase in his ability to fend for himself. Whereas on admission his feet had been so tender that washing them caused him much pain, only moderate caution was necessary in manipulation. He became able to stand, with assistance, for a few seconds at a time and was able to raise himself in bed without assistance.

In summary this was a forty-nine year old white Polish male with a history of asthma dating from September, 1946; neurologic findings dating from March 19, 1949, with acute exacerbation and marked neuropathic myopathic involvement of all extremities following a transfusion reaction on March 28, 1949. A diagnosis of periarteritis nodosa was confirmed by skin and muscle biopsy in April, 1949. The asthma regressed with the onset of his acute illness in March, 1949, and recurred in October, 1949.

It was decided that the patient should be given the opportunity of ACTH therapy, despite a poor prognosis for the neurologic condition. During the two weeks prior to therapy he suffered pain as usual in the shoulders, arms, hands, legs and feet. Asthmatic symptoms were severe. He had remained afebrile with the exception of two days. Sedimentation rates were over 100 mm. in one hour. The classical skin lesions of periarteritis nodosa[5] were noted for the first time. These were raised, firm, brownish-pink nodules, non-tender, movable, non-hemorrhagic, and measured about 0.5 cm. in diameter.

Two weeks prior to therapy he was placed on the Kempner rice diet, supplemented by 18 gm. of salt per day. This diet was thought to be the most stable one available for metabolic studies. He remained on this regimen throughout the first course of the drug. The dosage schedule of ACTH* was 25 mg. every six hours intramuscularly for two days and 10 mg. every six hours intramuscularly for the next five days. The ACTH was obtained in solid form and fresh solutions were prepared twice each day.

Pulmonary function studies were carried out on the day before therapy. The results of these studies, which were also conducted in conjunction with additional courses of ACTH and cortisone, will be discussed subsequently.

On October 20, 1949, a skin biopsy of the calf of the right leg, including typical periarteritic skin nodule, was performed. On the same day he was given his first injections of ACTH. On the second day of therapy the patient became euphoric. There was no diminution in pain but he felt that there was increased mobility of the left hand and he felt generally improved although objective signs of improvement were lacking. On the fourth day of therapy

* The ACTH used in this experiment (a product of Armour Laboratories) was supplied in part by a grant from the United States Public Health Service and through the courtesy of Dr. Charles Ragan.

general mobility was markedly increased. The biopsy wound appeared to be healing satisfactorily. On the fifth day there was decided improvement in his asthmatic symptoms although signs were still present in both lung fields. His euphoria increased with each day. By the seventh day no abnormal signs were present in the lungs. His asthma had undergone complete remission. The leg wound was excised *in toto* after seven days. Pathologic observations are reported elsewhere.[7]

Pain remained unchanged. No alteration was noted in the cutaneous skin nodules. He developed flight of ideas. His increased general mobility was obvious. Most marked was the response seen in both hands. The left hand, the dorsum of which was once board-like and rigid, was quite flexible. The fingers of the left hand could be flexed to touch the palm, twice the range of motion prior to therapy. The index and middle fingers of the right hand apparently developed enough strength to pick up objects with some facility and moderate power. This he had not been able to do since April, 1949. He began to take steps and walk without assistance.

Improvement continued after cessation of therapy. Eight days following therapy the patient was able to walk the distance of one-half block. He had not walked more than a few steps for seven months.

Asthmatic symptoms and signs returned approximately two weeks after the last dose of ACTH. His sense of well being suffered but little from the recurrence of these symptoms. There was no change in his pain threshold and according to the patient his increased activity was due to two things: (1), a feeling that he could conquer his pain and a sense of accomplishment in doing so; (2), a definite feeling of increased strength.

On November 15, 1949, the patient suffered a severe attack of asthma. At that time the erythrocyte sedimentation rate was 93 mm. in one hour, and the total eosinophil count was as high as 3,700 per cu. mm. Despite the obvious relapse of his asthma the patient remained afebrile and it was not believed that the underlying disease entity of periarteritis nodosa was exacerbated beyond the affects on the respiratory system. Asthmatic symptoms remained severe.

On December 12, 1949, he was given 100 mg. of ACTH. Within twenty-four hours the patient had become so euphoric and achieved such marked relief of asthmatic symptoms that the dosage was reduced to 40 mg. daily for the remainder of the one-week course. This seven-day regimen resulted in increased mobility of wrists and ankles and an obvious remission of asthma as corroborated by pulmonary function studies. Whereas the first course of ACTH had given dramatic clinical improvement the erythrocyte sedimentation rate remained elevated at 110 mm. in one hour. During this course the rate fell from 94 mm. in one hour to 32 mm. in one hour. Asthmatic remission remained for ten days. The erythrocyte sedimentation rate rose progressively over the remission period and was again 91 mm. in one hour. Prior to the first course of ACTH the serum albumin was 2.8 gm. per cent and the serum globulin 3.4 gm. per cent. Following the first course the serum albumin was 3.7 gm. per cent and the serum globulin 3.4 gm. per cent. Following this last course of ACTH the serum albumin was 3.5 gm. per cent and the serum globulin had fallen to 2.8 gm. per cent. No abnormalities of thymol turbidity had been noted and the cephalin flocculation test had remained negative.

Because of a febrile episode on January 29, 1950, it was believed that he had undergone an exacerbation of periarteritis nodosa. He was given ACTH 100 mg. daily for four days starting February 2, 1950. Asthmatic symptoms disappeared within the first eighteen hours. Pain in the hands and feet remained. The erythrocyte sedimentation rate fell to 40 mm. in one hour. On February 10, 1950, the white blood cell count was 8,400 per cu. mm. Asthmatic symptoms recurred fourteen days following the last dose of ACTH.

On February 21, 1950, the patient was started on a four-day course of ACTH, given 45 mg. daily. He had complained of coryza, a cough productive of one-fourth to one-half cup of clear mucoid sputum, and moderately severe asthmatic wheezing for several days. He obtained moderate relief of the asthmatic symptoms but wheezes were never completely absent. On the third day of therapy his temperature rose to 102°F. and he had several chills. Moist and mucoid rales were heard at the left base posteriorly and it was believed that the patient had a respiratory infection. He was given penicillin 500,000 units twice a day for five days. The temperature fell to normal on the second day of therapy. The erythrocyte sedimentation rate following the four-day course of

ACTH was 97 mm. in one hour. Following the febrile episode he coughed up approximately one-half cup per day of watery, greenish sputum. His asthmatic symptoms remained in moderate remission for a period of seven days following the last dose of ACTH.

The patient remained out of the hospital for three and one half months and was readmitted on October 2, 1950. During the interval he was seen by one of us (W. L. M.) at least once each week. There was no major change in his condition. He was able to walk for three blocks before being stopped by weakness in the lower extremities. Pain, described as a "burning and twisting sensation," was persistent and was confined to the extremities distal to the wrists and ankles. Grasp had been weak in both hands, more so in the left, and the right hand could not be fully closed. Skin nodules of periarteritis nodosa resembling those seen in the hospital appeared from time to time. He suffered one episode lasting two days which was marked by temperature to 102°F., nausea, anorexia, vomiting and an increase in asthmatic symptoms. He continued using adrenalin, aminophyllin and demerol, giving his own injections.

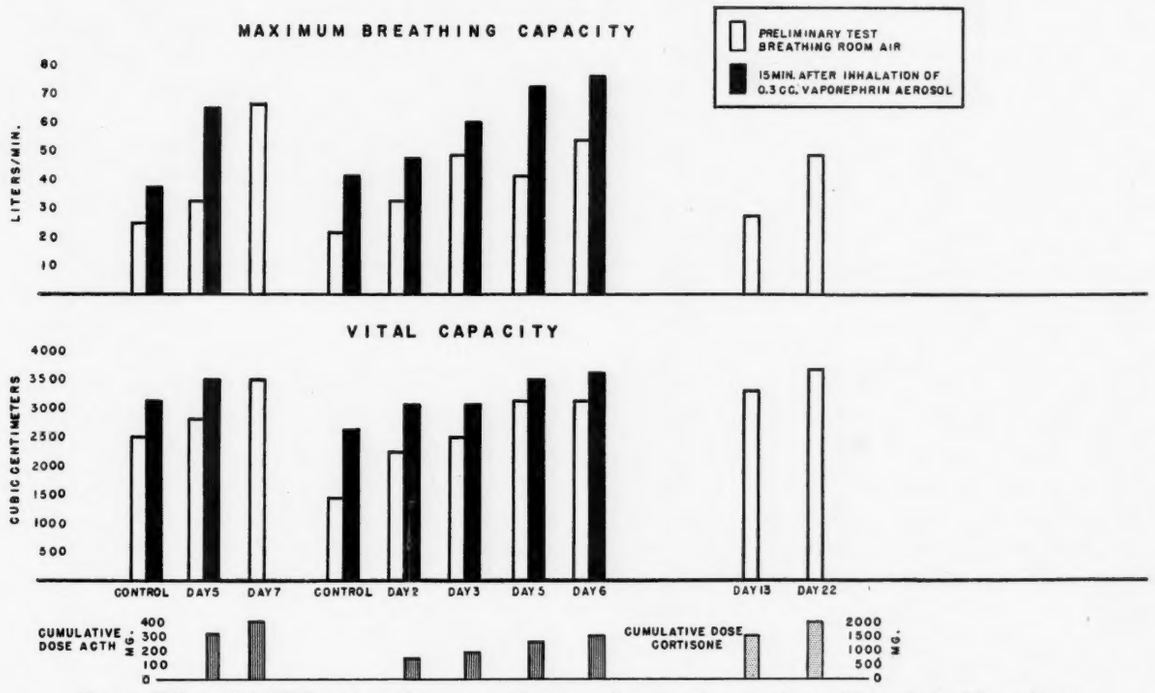


FIG. 1. Effect of ACTH and cortisone on pulmonary function in a patient with periarteritis nodosa.

Following recovery from the above acute episode the patient was given vaponephrin and penicillin aerosol therapy. Some relief was obtained but he still required adrenalin and aminophyllin for adequate relief of respiratory symptoms. His productive cough continued much the same. The results of the pulmonary function studies performed during the various courses of ACTH are recorded in Figure 1.

Asthma remained a major problem but over the period of the following three months he became fully ambulatory. Pain was always present to some degree in the hands and feet but it became less marked. Pertinent laboratory data shortly before discharge from the hospital in June, 1950, revealed an erythrocyte sedimentation rate of 54 mm. in one hour, blood urea nitrogen 24 mg. per cent, albuminuria 3 plus, phenolsulfonphthalein excretion 33 per cent in two hours and a 75 per cent normal urea clearance. Urine concentration was 1.022.

Physical examination on admission revealed no new findings. The patient's vital signs were normal at the time of admission and remained so during his entire hospital stay. There were no significant changes in the laboratory findings. During an eight-day control period the laboratory data were essentially stable with the excep-

tion of a drop in the erythrocyte sedimentation rate of 52 mm. in one hour on the second day, to 37 mm. in one hour on the eighth day. The patient was given a total of 1 gm. cortisone acetate during the first week of therapy, 75 mg. each day during the second week and was then adjusted to a dosage of 100 mg. on alternate days, supplemented by 3 gm. of potassium chloride each day.

The fifth day of cortisone therapy was the first day that he had spent entirely without adrenalin therapy since the recurrence of asthma which followed the last course of ACTH nine months before. His sputum changed in quality from thick, gray and mucoid to clear, white and watery. He estimated its daily volume to be one-third the pretreatment volume. After the ninth day of therapy he produced no sputum. Over the following ten days he noted a moderate diminution in calf tenderness. There was no change, however, in his neuropathic symptoms. A few skin nodules appeared on the fifth and the nineteenth days of therapy but were transient in nature, lasting from a few hours to several days. Whereas definite euphoria had occurred during the first two courses of ACTH, there was no change noted in mental attitude during cortisone therapy. Electromyograms showed definite evidence of lower motor neurone involvement and suggested ventral horn involvement as manifested by a significant degree of synchrony in single motor unit potentials recorded from two electrodes inserted into the same muscle.

Despite the persistence of pain in the patient's extremities, the maintenance of motor and sensory response and the lack of progression of muscular atrophy indicated to us that his neuropathy was not progressing.

Following discharge from the hospital in October, 1950, the patient was maintained with cortisone administered every other day, both orally and parenterally. Starting in January, 1951, he took 75 mg. of cortisone orally every other day. During February, 1951, he noted a progressive relapse of asthma and desired adrenalin for relief.

The dose of cortisone was not increased and it was decided to give him a "rest period." On the third day of this period he had a moderately severe asthmatic attack and was given 200 mg. ACTH over a four-day period. Ten days following cessation of cortisone and three days after the ACTH was stopped the patient suffered a marked reaction to 0.75 cc. adrenalin intramuscularly, with severe abdominal cramps and a "terrific pressure headache," followed by extreme weakness and profuse perspiration. The entire episode was transient and the cramps and headache disappeared within three to five minutes. Perspiration was marked for approximately one hour. The pulse was never over 90. It was believed that this reaction might be related to return of adrenal function from an assumed state of hypoactivity. The episode fell within the usual period of three to ten days reported to be necessary for return of adrenal sufficiency following cessation of prolonged courses of cortisone and independent of ACTH therapy.[20]

The patient was without cortisone for thirty-five days. He used 0.5 to 0.75 cc. adrenalin without incident. During this "rest" period he had two transient episodes of fever which did not respond to penicillin. Each episode lasted for several days during which he suffered from weakness, anorexia and a marked exacerbation of asthmatic symptoms. Cortisone therapy has now been reinstituted, again with favorable response.

COMMENTS

Extensive clinical reviews of periarteritis nodosa may be found in the literature.[1,5,9,31] Pertinent to this case is the evidence for a triad of periarteritis nodosa, asthma and marked eosinophilia of peripheral blood.[34] As a frequent component in the symptom complex of periarteritis nodosa, the patient exhibited intermittent, severe episodes of intractable asthma. In evaluating the effect of ACTH and cortisone on the asthmatic component of this disease, pulmonary function studies as described by Baldwin, Cournand and Richards[2] were performed. (Fig. 1.)

Control values for vital capacity and maximum breathing capacity were obtained before instituting therapy. The determinations were usually repeated fifteen minutes after the aerosol inhalation of 0.3 cc. of 2.25 per cent racemic epinephrine.

To determine the immediate effect of a single dose of ACTH on the ventilatory function, four tests were performed at hourly intervals following the first dose of 25 mg. ACTH. No significant change was observed in either vital capacity or maximum breathing capacity and the patient's clinical status was unaltered.

By the fifth day of the first course of ACTH considerable clinical improvement in the patient's asthma had become apparent. On the seventh day he was symptom-free. This was reflected by an increase of 42 per cent in the vital capacity and 155 per cent in the maximum breathing capacity. Remission continued for a period of two weeks after cessation of the drug. Gradual recurrence of asthma heralded the reactivation of his disease process and control studies performed prior to a second course of ACTH yielded lower values for vital capacity and maximum breathing capacity than in the first control period.

Response to the second course of ACTH was equally striking. Marked relief of asthma was obtained clinically within twenty-four hours. Remission persisted for ten days following this course. The effect of cortisone on the pulmonary function as represented by two studies revealed an increase in function similar to that obtained with ACTH.

Two case reports cited by Levin et al.[17] and Stillman[32] confirm in large measure our findings on the effect of ACTH on the asthmatic component of periarteritis nodosa. Bordley et al.[4] and Herschfus et al.[12] have also reported on the effects of ACTH on chronic, intractable bronchial asthma. In general, improvement was noted within four to forty-eight hours, the patient becoming symptom-free in four to five days. Relapse occurred in all patients who had been followed for two months or more. Tracings of the vital capacity and the expiratory phase showed improvement with removal of "the relative obstruction to out-flow." We have observed similar clinical responses in a total of forty-five patients treated with ACTH and cortisone.[3]

Schwartz[28] has treated three cases of intractable asthma with oral cortisone, obtaining comparable clinical relief to that seen when using intramuscular preparations. However, he noted more rapid recurrence of symptoms on cessation of therapy.

Follow-up reports on cases of periarteritis nodosa as long as twenty months following therapy with ACTH and cortisone lend support to a more encouraging outlook. Shick and associates[29,30] have treated thirteen patients with cortisone and ACTH. Two patients died; necropsy revealed widespread visceral infarction secondary to narrowing and thrombosis of healing vessels. One case with marked renal involvement and azotemia is currently under treatment. Follow-up reports on ten cases for periods up to twelve months since completion of treatment are available. One case relapsed five months following cessation of therapy with ACTH. Remission was again obtained and he has since been maintained with suppressive doses of cortisone. Nine patients have showed no definite evidence of relapse since treatment. Shick concludes that it is as yet too early to assume that ACTH and cortisone can induce permanent remissions in periarteritis nodosa.

The case reported by Goldman and associates[8,17] is still alive twenty months following two initial courses of ACTH. Since October, 1949, he has received two additional courses of ACTH for the control of bronchial asthma.

Stillman[32] reported a case with polyneuritis, pericarditis and cardiac failure which responded well to ACTH. The eight-week follow-up available to us gave evidence of a slow return of activity of the disease but less severe than pre-treatment.

Stillman and Bayles[33] treated two patients with ACTH. The first obtained a ten-week remission but the second patient relapsed immediately upon discontinuation of therapy.

A patient of Carey and associates[6] had a perforation of a Meckel's diverticulum during ACTH therapy. This same patient has received four intensive courses of ACTH. Prompt remission as well as prompt relapse attended each course.

SUMMARY

1. A case is presented of a fifty year old male with periarteritis nodosa complicated by bronchial asthma. The patient has been observed for two years.

2. Four separate courses of ACTH induced clinical improvement and temporary remissions of his disease processes.

3. Prolonged therapy with both oral and intramuscular cortisone in suppressive doses shows promise of maintaining remission.

REFERENCES

1. Arkin, A. A clinical and pathological study of periarteritis nodosa. A report of five cases, one histologically healed. *Am. J. Path.*, 6: 401, 1930.

2. Baldwin, E. deF., Cournand, A. and Richards, D. W. Pulmonary insufficiency. I. Physiological classifications, clinical methods of analysis, standard values in normal subject. *Medicine*, 27: 3, 1948.

3. Barach, A. L., Bickerman, H. A. and Beck, G. J. Unpublished data.
4. Bordley, J. E., Carey, R. A., Harvey, A. M., Howard, J. E., Kattus, A. A., Newman, E. V. and Winkenwerder, W. L. Preliminary observations on the effect of adrenocorticotropic hormone (ACTH) in allergic diseases. *Bull. Johns Hopkins Hosp.*, 85: 396, 1949.
5. Boyd, L. J. I. The clinical aspects of periarteritis nodosa. *New York M. Coll. Flower Hosp. Bull.*, 1: 219, 1938. II. The clinical aspects of periarteritis nodosa. *Ibid.*, 3: 32, 1940. III. Periarteritis nodosa. Cutaneous symptoms. *Ibid.*, 3: 175, 1940. IV. Periarteritis nodosa. Neuromyositic manifestations. *Ibid.*, 3: 272, 1940. V. Periarteritis nodosa. Abdominal manifestations. *Ibid.*, 4: 27, 1941. VI. The renal and cardiac manifestations of periarteritis nodosa. *Ibid.*, 4: 176, 1941. VII. The cerebral and ocular manifestations of periarteritis nodosa. *Ibid.*, 6: 130, 1943. VIII. Pulmonary manifestations of periarteritis nodosa. *Ibid.*, 7: 94, 1944.
6. Carey, R. A., Harvey, A. M. and Howard, J. E. The effect of adrenocorticotropic hormone (ACTH) and cortisone on the course of disseminated lupus erythematosus and periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 87: 425, 1950.
7. Creditor, M. C., Bevans, M., Mundy, W. L. and Ragan, C. Effect of ACTH on wound healing in humans. *Proc. Soc. Exper. Biol. & Med.*, 74: 245, 1950.
8. Goldman, R. Personal communication.
9. Harris, A. W., Lynch, G. W. and O'Hare, J. P. Periarteritis nodosa. *Arch. Int. Med.* 63: 1163, 1939.
10. Harvey, A. M., Howard, J. E. and Kattus, A. E. The effect of adrenocorticotropic hormone (ACTH) and cortisone on certain diseases of the eye in which hypersensitivity plays a role. *Bull. Johns Hopkins Hosp.*, 87: 461, 1950.
11. Hawn, C. V. Z. and Janeway, C. A. Histological and serological sequences in experimental hypersensitivity. *J. Exper. Med.*, 85: 571, 1947.
12. Herschfus, J. A., Levinson, S. and Segal, M. S. ACTH therapy in bronchial asthma. *Bull. New England M. Center*, 12: 4, 1950.
13. Howes, E. L. Personal communication.
14. Klemperer, P. Diseases of the collagen system. *Bull. New York Acad. Med.*, 23: 581, 1947.
15. Klemperer, P. The pathogenesis of lupus erythematosus and allied conditions. *Ann. Int. Med.*, 28: 1, 1948.
16. Klemperer, P., Pollack, A. B. and Baehr, G. Pathology of disseminated lupus erythematosus. *Arch. Path.*, 32: 569, 1941.
17. Levin, M. H., Adams, W. S., Beck, W. S., Goldman, R. and Bassett, S. H. Prolonged treatment of a case of periarteritis nodosa with ACTH: the effective dose as measured by metabolic balances. *J. Clin. Endocrinol.*, 11: 375, 1951.
18. Longcope, W. T. Serum sickness and analogous reactions from certain drugs particularly the sulfonamides. *Medicine*, 22: 251, 1943.
19. Ragan, C. Effect of ACTH and cortisone on connective tissue: discussion on page 148 of Ragan, C., ed. Connective Tissues. Transactions of the First Conference, April 24–25, 1950, New York, N. Y. New York, 1951. Josiah Macy, Jr., Foundation.
20. Ragan, C. Personal communication.
21. Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., Blunt, J. W. and Lattes, R. The effect of ACTH and cortisone on connective tissue. *Bull. New York Acad. Med.*, 26: 251, 1950.
22. Rich, A. R. The role of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.*, 71: 123, 1942.
23. Rich, A. R. Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa. Another case associated with a sulfonamide reaction. *Bull. Johns Hopkins Hosp.*, 71: 375, 1942.
24. Rich, A. R. Hypersensitivity to iodine as a cause of periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 77: 43, 1945.
25. Rich, A. R. Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis. *Harvey Lect.*, 42: 106, 1946.
26. Rich, A. R. and Gregory, J. E. The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.*, 72: 65, 1943.
27. Rose, B., Pare, J. A. P., Pump, K. and Stanford, R. L. Preliminary report on adrenocorticotropic hormone (ACTH) in asthma. *Canad. M. A. J.*, 62: 6, 1950.
28. Schwartz, E. Oral cortisone in intractable bronchial asthma. *J. Allergy*, 22: 1, 1951.
29. Shick, R. M. Personal communication.
30. Shick, R. M., Bagenstoss, A. H. and Polley, H. F. The effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis: preliminary report. *Proc. Staff Meet., Mayo Clin.*, 25: 135, 1950.
31. Spiegel, R. Clinical aspects of periarteritis nodosa. *Arch. Int. Med.*, 58: 993, 1936.
32. Stillman, J. S. Discussion on the effect of ACTH on one case of periarteritis nodosa. Fed. Proc. First Clinical ACTH Conf., Mote, H. R., Philadelphia, 1950. Blakiston Co.
33. Stillman, J. S. and Bayles, T. B. Cited in: Thorn, G. W. et al. *New England J. Med.*, 242: 783, 824, 1950.
34. Wilson, K. S. and Alexander, H. L. The relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. *J. Lab. & Clin. Med.*, 30: 195, 1945.
35. Woods, A. C. and Wood, R. M. The action of ACTH and cortisone on experimental ocular inflammation. *Bull. Johns Hopkins Hosp.*, 87: 482, 1950.

Trichinosis*

Case Report with Observations of the Effect of Adrenocorticotropic Hormone

WILLIAM MABON DAVIS, M.D. *and* HARRY MOST, M.D.
New York, New York

TRICHINOSIS in man has been variously estimated to have occurred in from 2.4 to 30 per cent of the general population of the United States.[1–4] The vast majority of these cases are unrecognized and untreated. Severe trichinosis is a relatively rare occurrence. The lack of any specific therapy has made the management of patients with severe trichinosis a difficult problem. The opportunity to observe a case of acute, almost overwhelming trichinosis was utilized to ascertain the possible beneficial effects of adrenocorticotropic hormone (ACTH) in the course of the disease. The following case report is presented:

CASE REPORT

R. H., a forty-three year old male, was admitted to the Third Medical Division (New York University) of Bellevue Hospital on January 15, 1951, with a chief complaint of nausea and vomiting. The onset of the present illness began with these complaints which developed suddenly seven days prior to admission shortly after the ingestion of a meal of creamed herring and cold beer. General malaise appeared followed with chilly sensations. The malaise was described as vague, ill defined muscular aches and fatigue. The following day a shaking chill and fever developed. The malaise and nausea increased and the patient began to vomit. The family physician saw the patient on the third day of the illness and prescribed paregoric for "acute gastroenteritis." The vomiting continued with frequent retching; no diarrhea developed. Several days before admission bilateral subconjunctival hemorrhages appeared.

At the time of hospital admission the consumption of raw or poorly cooked pork was denied. Subsequently it was ascertained that the patient was frequently accustomed to preparing and eating raw hamburger sandwiches. The last such ingestion could not be dated with certainty. None of the other members of the household had eaten raw meat and none had become ill.

Physical examination at the time of admission revealed the patient's temperature to be 103.2°F., pulse 100, respiration 18 and blood pressure 140 systolic and 80 diastolic. The patient was acutely ill and appeared fatigued. Extensive bilateral subconjunctival hemorrhages were striking. Minimal periorbital edema was noted. The remainder of the physical examination was within normal limits.

Laboratory findings on admission included the following: The urine showed a specific gravity of 1.031 and 2 plus albuminuria but was otherwise negative. The hemoglobin was 14.5 gm. per cent and the red blood count 5,980,000. The white blood count was 18,850; the differential showed 88 per cent polymorphonuclear cells. The platelet count was 457,000 per cu. mm. The Rumpel-Leeds test was negative and clotting and bleeding times were normal. The prothrombin time was 16 seconds (control 17 seconds). The blood non-protein nitrogen determination was 30 mg per cent. The total serum protein was 5.9 gm. per 100 cc. with an albumin of 4.1 gm. and globulin of 1.8 gm. The icteric index was 3. The cephalin flocculation test was 3 plus. The serum cholesterol was 143 mg. per cent and the alkaline phosphatase 1.5 Bodansky units per 100 cc. Blood, sputum, nose and throat, and stool cultures were negative. The spinal fluid was examined and cultured on the third hospital day and was not remarkable. Examination of stool for ova and parasites was negative.

* From the Departments of Medicine and Preventive Medicine, New York University College of Medicine, and the Third (NYU) Medical Division of Bellevue Hosptial, New York, N. Y.

On the fourth hospital day the white blood count was 20,650, of which 40 per cent were eosinophilic granulocytes. The trichinella skin test was negative; specimens of blood were laked and examined for larvae of Trichinella spiralis with negative results; two additional specimens of spinal fluid were normal and the centrifuged sediment revealed no larvae. A muscle biopsy on the nineteenth day of hospitalization confirmed the diagnosis of trichinosis. The electrocardiogram was normal. Chest x-ray was not remarkable.

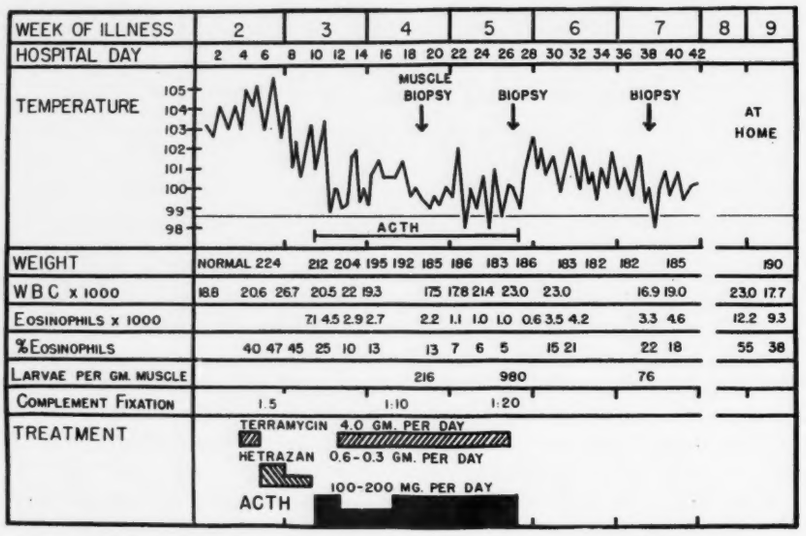


FIG. 1. Clinical and laboratory features; acute trichinosis; ACTH therapy.

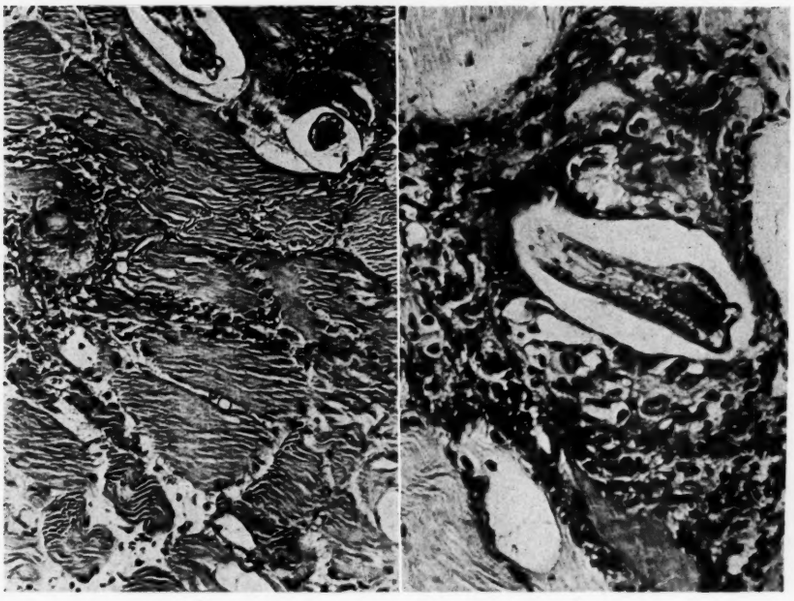
The significant features in the clinical and laboratory course of the infection are depicted graphically in Figure 1. Because of cough and diffuse pulmonary signs interpreted as indicating acute bronchitis and possible bronchopneumonia a brief course of terramycin was administered without effect. The daily dosage was 4.0 gm. The temperature was slightly lower during a five-day trial of hetrazan in a dosage of 0.3 to 0.6 gm. per day by mouth. During this entire period the patient remained acutely ill and appeared to be worse. There was profuse sweating and frequent vomiting and retching. Oral intake of fluids was negligible. Edema of the extremities and face appeared and was aggravated by assumed posture; edema of the right arm and leg increased if the patient remained on the right side for a period of several hours. The patient was apprehensive, restless, confused and partially disoriented at certain times. He presented evidence of exhaustion and fatigue. A sense of obstruction in the upper esophagus and posterior pharynx developed but direct examination revealed no abnormality.

Because of deterioration in the patient's general condition and to observe the effect of ACTH in this disease ACTH was started on the tenth hospital day in a dosage of 200 mg. per day on a schedule of 50 mg. every six hours. The dose was decreased to 100 mg. per day for three days and increased again to 200 mg. per day for the remainder of the course. The total ACTH administered over seventeen days was 2,950 mg. The following changes not indicated graphically (Fig. 1) occurred during the seventeen day course of ACTH administration:

There was dramatic subjective improvement in the patient. He was no longer restless and confused although he remained weak and fatigued. His appetite improved and adequate oral intake of food and fluid became possible for the first time. There was an accompanying fall in temperature.

Muscle biopsy of the right gastrocnemius muscle (Fig. 2) was performed on the nineteenth day of hospitalization and ninth day of ACTH administration. Teased pressed preparations showed numerous viable larvae of T. spiralis. Digestion revealed a parasite count of 216 larvae per gram of muscle tissue. Histologic sections showed considerable interstitial edema and an infiltration of inflammatory cells, chiefly mononuclear cells, lymphocytes and polymorphonuclear cells. A number of coiled larvae were identified.

A second biopsy of the left gastrocnemius



2A 2B

FIG. 2. Muscle biopsy, ninth day of ACTH administration. A, this illustrates the diffuse myositis and shows two unencysted young larvae of T. spiralis. Hematoxylin and eosin, approximately × 400. B, this demonstrates the inflammatory and granulomatous reaction occurring around a larva. Hematoxylin and eosin, approximately × 900.

muscle (Fig. 3) on the seventeenth day of ACTH administration again showed numerous larvae, the number being 980 larvae per gram of muscle. The histologic sections showed moderate diminution in the extent of edema and inflammatory cell infiltration. A significant number of these cells were eosinophilic granulocytes.

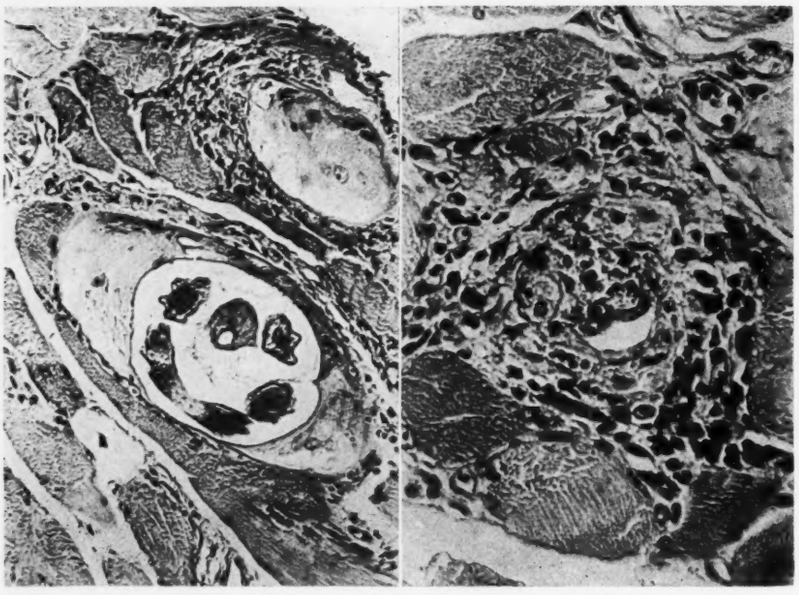
Finally, a third muscle biopsy (Fig. 4) was obtained on the thirty-eighth day of hospitalization and twelve days after cessation of ACTH administration. Viable larvae were again demonstrated. The larval count was 76 per gram of muscle. The histologic picture was again that of diffuse myositis with considerable inflammatory cell infiltration. Numerous parasites could be seen. Eosinophilic granulocytes were strikingly few among the inflammatory cells.

Because of recurrence of cough and moderate dyspnea and findings of pulmonary wheezes and rhonchi thought again to indicate acute tracheobronchitis or bronchopneumonia the patient received terramycin in dosage of 4.0 gm. per day during most of the course of ACTH. On this regimen the symptoms and signs of pulmonary disease cleared gradually over several days.

The electrocardiogram was recorded on five separate occasions and failed to show any significant changes. The venous pressure and circulation times were normal. No clinical or roentgenologic evidence of cardiac enlargement occurred.

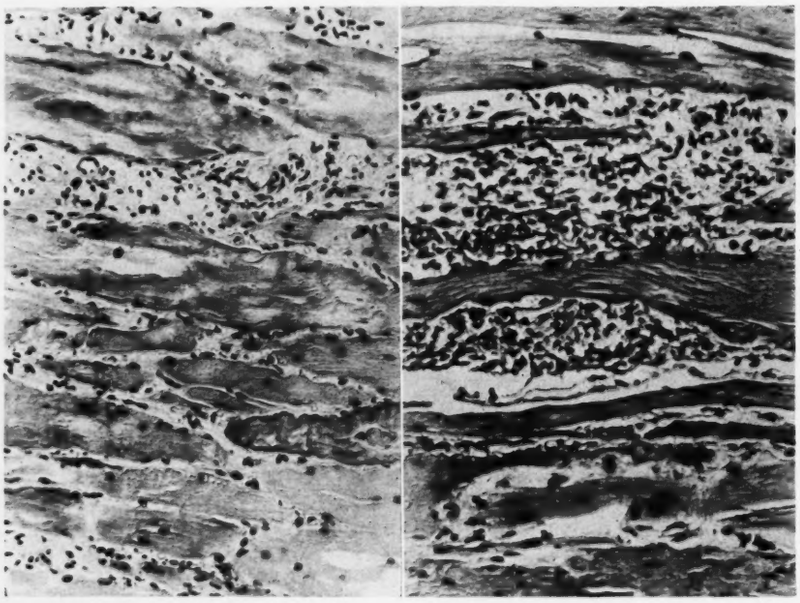
During the height of the patient's illness, just before and with the administration of ACTH, hepatomegaly appeared and gradually receded in two weeks' time.

The subjective improvement which occurred while ACTH was administered continued during the period following its cessation. The patient was ambulatory and had a good appetite; he continued to be weak and felt exhausted. The feeling was described by the patient as similar to that occurring after very strenuous exercise. With cessation of therapy there was no clinical exacerbation other than fever. On February 20, 1951, after six weeks in the hospital, the patient was discharged for convalescence at home. He was seen once or twice weekly thereafter. An interesting development during this early convalescent period was the occurrence of migratory thrombophlebitis involving the superficial small veins of the wrist and forearms. This subsided spontaneously after several weeks. Further weight gain continued. The weakness and exhaustion lessened gradually. After four weeks at home the patient began part time work in a



3A 3B

FIG. 3. Muscle biopsy, sixteenth day of ACTH administration. A, this illustrates beginning encystment of two larvae and moderate inflammatory reaction. Hematoxylin and eosin, approximately × 200. B, this shows a localized area of inflammatory reaction and granuloma formation. A significant number of these inflammatory cells are eosinophils. Hematoxylin and eosin, approximately × 900.



4A 4B

FIG. 4. Muscle biopsy, twelve days after completion of the course of ACTH. A, this photomicrograph illustrates striking interstitial edema and a diffuse myositis. Hematoxylin and eosin, approximately × 200. B, this shows the inflammatory reaction occurring; few of these cells are eosinophils. Hematoxylin and eosin, approximately × 400.

radio repair shop and after twelve weeks returned to full time work again as a taxidriver.

COMMENTS

The findings and course in this case are compatible with similar findings in acute severe trichinosis.[5–7] Attempts have been made to correlate the course and severity of the illness and the prognosis with the degree of parasitic infestation. It would appear that fair correlation does occur although deaths[4] have occurred with muscle parasite counts as low as 111 larvae per gram of muscle and patients[5] have survived infestations with as many as 1,000 larvae per gram of muscle. In relation to the levels found in a series of cases recorded by Hall and Collins[3] this case should be considered a severe case of trichinosis. Because of the small amounts of muscle digested and examined parasite counts in patients are subject to considerable inaccuracy. This is well illustrated by our patient whose larval counts were consecutively 216, 960 and 76 per gram of muscle tissue. In the period of muscle invasion there should actually be a continuous rise in the parasite count both absolute in terms of total muscle bulk and per unit of muscle tissue.

The use of hetrazan (1-diethylcarbamyl-4 methylpiperazine hydrochloride) in our patient requires brief comment. This drug has been used with some success against the migratory filarial forms of Wuchereria bancrofti, Loa loa and onchocerca in both experimental infections and in patients.[8–11] It is not effective against the adult parasites and depends for its effects upon the phagocytosis of filarial forms by cells of the reticuloendothelial system. Oliver-Gonzalez and Hewitt[12] report the use of hetrazan in experimental trichinosis. The number of adult trichinae in the intestines of treated rats was significantly reduced as compared to control untreated rats. Similarly, the number of larval forms in the muscle of treated rats was considerably lower than that of untreated rats when they were examined thirty days following infection. In our patient hetrazan was used for three days only and discontinued in order to assess the effect of ACTH. The period of trial with hetrazan was too brief to evaluate its effect.

Terramycin was administered initially without effect on the course of the infection. Its use shortly after starting ACTH and during the course of ACTH was dictated by evidence of pulmonary infection. Improvement clearly began before its use.

Prior to the administration of ACTH it was considered quite possible that the infection would be lethal. The relatively dramatic subjective improvement, accompanied with a less well-defined fall of temperature which occurred concomitantly with the use of ACTH, suggests that ACTH was beneficial in this instance.

The response of the blood levels of eosinophils during the administration of ACTH confirms the observations of Morales, Caras and Sanz[13] in regard to the eosinophil drop occurring after the Thorn test (epinephrin) in patients with eosinophilia due to parasitic infection. In a personal communication[14] Dr. Norman Shumway has informed us of another case of trichinosis treated with cortisone during the sixth week of illness when the patient was in the convalescent period. The eosinophil count, which was 1,700 per cu. mm., fell slowly over a two-week period to 200 where it remained for one month during further treatment. Because of the stage of the disease in which the cortisone was used he is unable to state whether any benefit occurred from its use.

As shown graphically (Fig. 1), there was progressive rise of antibodies as measured by the complement fixation test. In a personal communication[15] Dr. John Bozicevich has stated that this rise indicates no impairment of antibody production.

The histologic preparations obtained serially during and subsequent to the administration of ACTH (Figs. 2 to 4) showed that muscle invasion was unaffected by ACTH but that the acute inflammatory process occurring with this invasion, particularly the diffuse myositis, was altered. With cessation of ACTH the diffuse myositis again became prominent. The evidence is insufficient to state whether the process of larval encystment was in any way modified by the use of ACTH. There was no evidence of larvicidal effect.

The benefit to be ascribed to ACTH came in all probability as a result of non-specific effects. There is no therapeutic agent at present which clearly has the following properties: the ability to affect the adult parasites during copulation, gestation and burrowing, or the ability to affect the larvae during the phase of muscle invasion. However, in ACTH or cortisone we appear to have agents capable of modifying the body's

reaction to the invasion of muscle by the larvae or to their products.

SUMMARY

A case report of a patient with severe acute trichinosis is presented. The patient was observed before, during and after a period of administration of ACTH.* Clinical improvement occurred coincident with the use of ACTH and was for the most part sustained during the period following its use.

Observations of the extent and character of the muscle invasion and concomitant diffuse myositis were made and are discussed. The eosinophilia so characteristic of the disease fell slowly during the administration of ACTH. Progressive rise of antibodies occurred.

It is believed that distinct benefit occurred as a result of the course of ACTH. The possible mechanisms of its action in trichinosis are briefly discussed. It is suggested that ACTH be tried in future cases of trichinosis to assess further its possible beneficial role.

Acknowledgment: The authors wish to acknowledge their indebtedness to Dr. Sigmund Wilens for the photomicrographs and review of histologic material, Dr. John Bozicevich for the performance of complement fixation tests and Mr. John Goeller for photographic assistance.

REFERENCES

1. McNaught, J. B. and Anderson, E. V. The incidence of trichinosis in San Francisco. *J. A. M. A.*, 107: 1446, 1936.
2. Hall, M. C. and Collins, B. J. Studies on trichinosis. I. The incidence of trichinosis as indicated by postmortem examination of 300 diaphragms. *Pub. Health Rep.*, 52: 468, 1937.
3. Hall, M. C. and Collins, B. J. Studies on trichinosis. II. Some correlations and implications in connection with incidence of trichinosis found in 300 diaphragms. *Pub. Health Rep.*, 52: 512, 1937.
4. Nolan, M. O. and Bozicevich, J. The incidence of trichinosis in adults by postmortem examination of 1000 diaphragms. *Pub. Health Rep.*, 53: 652, 1938.
5. Gould, S. E. Trichinosis. Springfield, Ill., 1945. Charles C Thomas.
6. Von Cott, J. M. and Lintz, W. Trichinosis. *J. A. M. A.*, 62: 680, 1914.
7. Wright, W. H. A consideration of the clinical and public health aspects of trichinosis. *Journal Lancet*, 62: 389, 1942.
8. Santiago-Stevenson, D., Oliver-Gonzales, J. and Hewitt, R. I. Treatment of Filariasis bancrofti with 1-diethylcarbamyl-4-methylpiperazine hydrochloride ("hetrazan"). *J. A. M. A.*, 135: 708, 1947.
9. Hawking, F., Sewall, P. and Thurston, J. P. Mode of action of hetrazan in filariasis. *Lancet*, 2: 730, 1948.
10. Hawking, F. and Laurie, W. Action of hetrazan on filariasis and onchocerciasis. *Lancet*, 2: 146, 1949.
11. Murgatroyd, F. and Woodruft, A. W. Loiasis treated with hetrazan (banocide). *Lancet*, 2: 147, 1949.
12. Oliver-Gonzales, J. and Hewitt, R. I. Treatment of experimental intestinal trichinosis with 1-diethylcarbamyl-4-methylpiperazine hydrochloride (hetrazan). *Proc. Soc. Exper. Biol. & Med.*, 66: 254, 1947.
13. Morales, F. H., Casas, Ç. B. and Sanz, M. G. Thorn test in patients with eosinophilia related to parasitic infection; preliminary report. *J. A. M. A.*, 144: 379, 1950.
14. Shumway, N. P. Personal communication.
15. Bozicevich, J. Personal communication.

* The ACTH used in this study was supplied by The Armour Laboratories through the courtesy of Dr. Albert H. Holland, Jr., Medical Director.

Infarction of the Stomach*

Report of Three Cases of Total Gastric Infarction and One Case of Partial Infarction

ELI B. COHEN, M.D.

Los Angeles, California

THE extreme rarity of total gastric infarction is evident after an extensive review of the literature which fails to reveal a heretofore reported case. Textbooks of pathology make no mention of this entity. They refer only to small areas of hemorrhagic infarction secondary to embolism or thrombosis as an etiologic factor in the genesis of peptic ulcer. Mallory,[1] Pack,[2] Popper,[3] Rich,[4] Callender[5] and Broders[6] state they have not encountered this lesion. If one discounts minute hemorrhagic erosions of the gastric mucosa, lesser degrees of infarction are likewise unusual. From the 23,836 autopsies performed from January 1, 1938, to April 30, 1950, at the Los Angeles County General Hospital three cases of complete and one case of partial infarction of the stomach have been culled.

Baumann,[7] Manfrini and Gerundini,[8] Platt,[9] Halbron et al.,[10] Mallory[1] and Popper[3] reported cases of partial gastric infarction. Baumann[7] in 1909 reported the first case of gastric infarction of any major degree. He described it as an incidental occurrence in an autopsy of a ninety year old woman. An area of about the size of the palm of a hand was hemorrhagic and extended 2 cm. above the pyloric sphincter. This area showed involvement of the muscularis only in a few places. The left and right gastric arteries and the right gastroepiploic artery, as well as some of the larger branches of these vessels, had been occluded by an adherent thrombus. Manfrini and Gerundini[8] report a case occurring in a boy four years of age who four months prior to death had a severe accidental burn. A large zone of hemorrhagic infarction along the greater curvature of the stomach with perforations was found. The authors postulated a disturbance in the circulation although they were unable to demonstrate embolism or thrombosis as the etiologic factor. Platt[9] described a case of a fifty-six year old woman in whom there was an 8.5 cm. area of gangrenous change in the upper third of the lesser curvature as a result of venous thrombosis. One of the tributaries of the coronary vein situated in this area was completely filled by a fairly recent antemortem clot. Halbron et al.[10] reported a case of multiple small gastric infarctions secondary to subacute thrombophlebitis of the portal system. Mallory[1] recalls a case of infarction of the remaining half of the stomach subsequent to resection of the fundic half. Popper[3] has seen small circumscribed areas of gastric infarctions in cases of portal thrombosis with cirrhosis of the liver but never involving the entire stomach.

CASE REPORTS

CASE I. B. M. P., a seventy year old Caucasian woman, was admitted to the Los Angeles County Hospital on July 22, 1948. Apparently she had enjoyed good health until two weeks prior to admission when she suddenly felt dizzy, weak and confused. One week later nausea and vomiting developed which persisted. She had no bowel movement following the onset of her illness. An emesis of "coffee ground" material occurred the day before entry.

Physical examination revealed a well developed, acutely ill woman with a temperature of 100°F., pulse 94, respiration 20 and blood pressure 210/110. The skin was warm and dry. Her chest was emphysematous and there were basal crepitant rales bilaterally. The heart was enlarged 1 cm. beyond the mid-clavicular line. No murmurs were heard. Auricular fibrillation was noted, with a ventricular rate of 94 per

* From the Department of Internal Medicine, College of Medical Evangelists, and the Los Angeles County Hospital., Los Angeles, Calif.

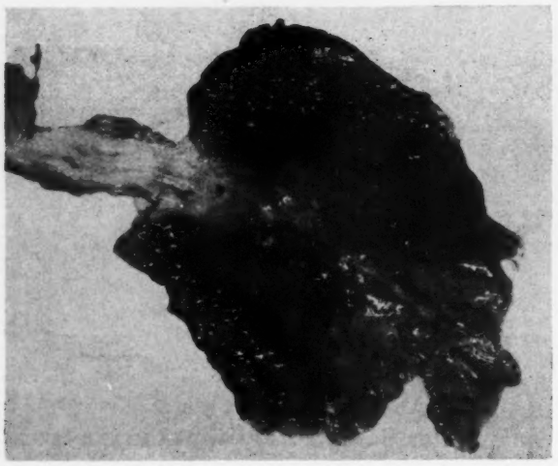


FIG. 1. The stomach opened along its greater curvature showing the hemorrhagic character of the infarction along the greater curvature. Note the pallor along the "Magenstrasse."

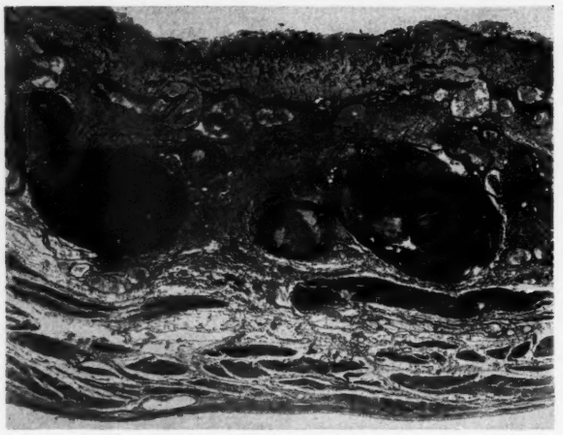


FIG. 2. Photomicrograph of section through the stomach shown in Figure 1. Note the engorgement and thromboses of the vessels. The entire wall shows coagulation necrosis.

minute. The abdomen was distended, tympanitic and diffusely tender. Peristalsis was hyperactive. No masses were palpable in the rectum. Laboratory procedures revealed a hemoglobin of 14 gm. per cent, a red blood count of 3.98 million and white blood count of 13,600 with 85 per cent polymorphonuclears. The non-protein nitrogen was 52 mg. per cent, CO_2 33 volumes per cent and plasma chlorides 532 mg. per cent. The electrocardiogram showed left ventricular hypertrophy and auricular fibrillation. Sigmoidoscopic examination was negative. A barium enema suggested possible obstruction at the hepatic flexure.

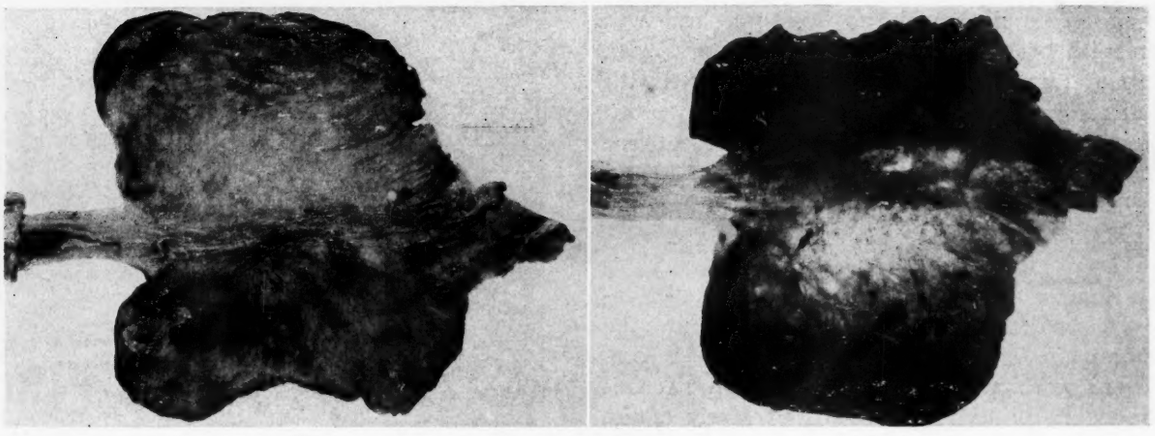
The abdominal distention was somewhat relieved by a Harris tube with Pottenger suction; the patient seemed slightly improved. On the fourth hospital day her abdomen became more distended and tender and a cecostomy was performed under local anesthesia. Exploration was not deemed advisable because of the patient's poor condition. Six hours following surgery she became comatose, her blood pressure dropped to 100/60 and in spite of transfusions and supportive care she expired.

Autopsy was performed eighteen hours after death. The heart weighed 460 gm.; there was moderate dilatation of the right and left ventricles. The right ventricle measured 5 mm. in thickness and the left, 15 mm. The free margins of the mitral and tricuspid valves were slightly atheromatous. The coronary arteries were moderately sclerotic with narrowing of the right coronary artery. The aorta was markedly sclerotic and an antemortem thrombus completely occluded the celiac axis. The splenic artery throughout its length and the first portion of the hepatic artery were occluded by thrombus formation. The lungs were heavier than normal and congested. The entire stomach was purplish red and appeared grossly infarcted. (Fig. 1.) The lesser curvature was slightly less hemorrhagic than the greater curvature. The first portion of the duodenum, cecum, ascending bowel and first portion of transverse colon were similarly infarcted. The liver weighed 1,380 gm. and on cut section showed patchy areas of infarction, the largest measuring 2 by 3 cm. The spleen was almost totally infarcted and weighed 140 gm. Both kidneys showed multiple areas of infarction. Histologically sections of the bowel, duodenum, liver, spleen and kidneys showed infarction.

Sections of the stomach (Fig. 2) microscopically showed the entire wall to be infarcted. The small vessels were distended and filled with blood, some containing thrombi.

Anatomic diagnoses were as follows: hypertensive heart disease; congestive heart failure; coronary sclerosis; embolus of the celiac axis; infarction of stomach, duodenum, large bowel, spleen, liver and kidneys; chronic pleuritis; generalized atherosclerosis, severe; simple cyst of ovary; fibromyomata uteri; and hemorrhagic cystitis.

CASE II. J. A., a sixty-three year old Mexican male, was admitted to the Los Angeles County Hospital on October 20, 1948. Eight to nine months prior to admission he had noted increasing exertional dyspnea, orthopnea, abdominal pain and swelling of his ankles. A cardiac regi-



3 4

FIG. 3. Serosal surface of stomach showing the extent of the infarction.
FIG. 4. Mucosal surface of stomach seen in Figure 3, showing the intense hemorrhagic character of the infarction along the greater curvature as compared with the anemic lesser curvature.

men had been instituted five months previously, and five years previously he had been hospitalized for "lung trouble."

Physical examination revealed a markedly dyspneic, orthopneic male. Blood pressure was 130/80 and pulse 80. The neck veins were distended and there were bilateral inspiratory rales. Heart sounds were inaudible. The abdomen was distended, a distinct fluid wave was present and the liver edge was palpated. There was marked edema of the lower extremities and abdominal wall. Laboratory tests showed a hemoglobin of 17 gm. and a white blood cell count of 9,100. Non-protein nitrogen varied from 75 to 105 mg. per cent. The albumin-globulin ratio was 3.2/3.6 and the CO_2 was 59 volumes per cent. Numerous electrocardiograms showed evidence of old anteroseptal infarction with Wenckebach's phenomenon. Chest x-ray revealed a right middle lobe rarefaction with a fluid level and marked emphysema.

The patient improved and appeared to be well compensated. However, on November 1, 1948, he began a gradual downhill course. Evidence of cardiac failure increased and he expired following a sudden massive hemorrhagic diarrhea on November 16, 1948. Autopsy was performed six and a half hours after death. The heart weighed 370 gm. The right ventricle and atrium were markedly dilated; the right ventricular wall measured 6 mm. in thickness and the left, 13 mm. The right auricular appendage contained a thrombus. The valve leaflets were normal. The aorta showed a marked degree of atherosclerosis with ulcerative changes. There was an adherent thrombus distal to the origin of the left renal artery which measured 1 by 2 cm., and a thrombus partially occluding the origin of the common iliacs at the bifurcation. The major branches of the aorta were markedly atherosclerotic but the celiac axis and its main branches and the branches of the superior and inferior mesenteric arteries were free of emboli, thrombi or atheromas. The right pleural space contained 1,000 cc. of turbid yellow fluid; the left 300 cc. There were dense fibrous adhesions at the left base anteriorly and right apex posteriorly and a massive pleural thickening over the right middle lobe laterally. The left lung weighed 335 gm. and the right, 520 gm. They were massively distended and the right contained a well encapsulated non-communicating abscess measuring 2 by 3 cm. in greatest diameters. The cavity was devoid of contents. The remaining lung tissue contained numerous recent infarcts, the largest measuring 10 cm. in diameter corresponding to clearly demonstrable thromboemboli in many of the major arteries. The pulmonary arteries showed a marked degree of atheromatous degeneration. The entire abdominal portion of the alimentary canal was a brownish red and purplish red color characteristic of infarction; this included the entire stomach (Figs. 3 and 4), small bowel, colon and rectum. The gastric mucosa was extremely hemorrhagic and necrotic in areas, particularly along the greater curvature where the infarction extended to the serosal surface. The intestinal tract was similarly involved. There were no thrombi in the portal vein or its tributaries. The mesentery and peritoneum were edematous, with areas of congestion and hemor-

rhage. The liver weighed 750 gm. and was greenish brown with patchy areas of yellowish brown mottling. It was flabby but cut with resistance, suggestive of fibrosis. The spleen weighed 55 gm. The parenchyma was raspberry colored and extremely firm, characteristic of passive congestion. The kidneys together weighed 270 gm. and were severely congested.

Histologically the sections through various portions of the stomach showed edema, thrombosis, early necrosis and hemorrhage into the submucosa, mucosa, muscularis and serosa. There were areas where coagulation necrosis extended throughout the various layers of the gastric wall. The liver and spleen microscopically showed severe chronic passive congestion; the lung abscess wall was composed of dense fibrous connective tissue with chronic inflammatory cells including the giant cells of Langhan's type.

Anatomic diagnoses were as follows: cor pulmonale; congestive failure; pulmonary emphysema; lung cyst, right middle lobe, chronic; pleuritis, chronic, adhesive; atherosclerosis, pulmonary; thromboembolism, pulmonary arteries; infarcts, pulmonary, multiple; mural thrombosis, right auricle; pericarditis, acute, fibrinous; infarction of stomach, small bowel and colon, including sigmoid; jaundice; atherosclerosis, local, coronary arteries; and prostatism, acute, with abscess formation.

Case III. E. C., a sixty-eight year old white woman, was admitted to the Los Angeles County Hospital on December 7, 1947. Nine hours prior to entry and again four hours later she had vomited clots of blood and passed bloody stools. Pain in the right lower thorax anteriorly, radiating to the right flank, had developed simultaneously. Anorexia, bouts of tarry stools and vomiting between meals had begun one week previously. She had been taking digitalis for the past four to five years because of shortness of breath. Hypertension and nocturia of two to three times had been present for the same length of time.

Physical examination revealed a poorly nourished woman in distress. She was poorly oriented, inattentive, restless and uncooperative. Her skin was cold and clammy. Her temperature was 98.6°F., pulse 110, respiration 18 and blood pressure 210/165. The neck veins were not distended and the lungs were clear. The heart was slightly enlarged beyond the midclavicular line. An apical, grade 2 systolic murmur was present. There was regular sinus rhythm, P-2 was greater than A-2. The abdomen was diffusely tender, more marked in the epigastrium and left lower quadrant. There were no audible peristalses. There were no abdominal masses. Peripheral edema was absent. The reflexes were hypoactive and a left Babinski sign was present. The laboratory studies revealed a hemoglobin of 17.5 gm. and a white count of 16,800 with 82 per cent polymorphonuclears and 18 per cent lymphocytes. The patient became comatose eight hours after admission. Loud rhonchi and rales developed rapidly; she became markedly cyanotic and expired within a few minutes.

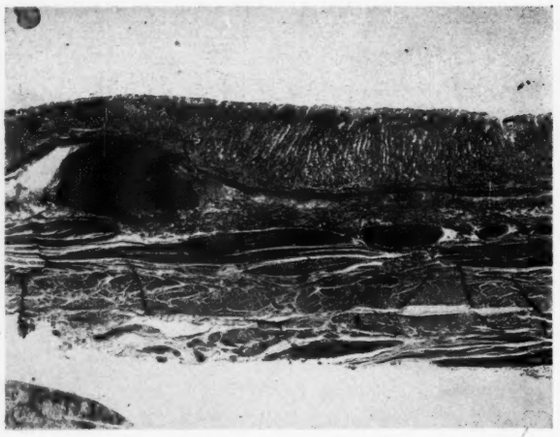


Fig. 5. Photomicrograph of section from stomach of Case III, showing thrombosed vessel and coagulation necrosis of the muscular layers.

Autopsy was performed six and a half hours after death. The heart was greatly enlarged and weighed 600 gm. The left ventricular wall measured 15 mm. and the right ventricle, 3 mm. The valves were normal. The aorta showed a moderate degree of atherosclerosis, particularly in the abdominal portion. Just below the celiac axis orifice there was a large arteriosclerotic aneurysm which extended down to 2 cm. above the origin of the iliac arteries. The lungs weighed 450 gm. each and were edematous. The peritoneal cavity contained approximately 25 cc. of bloody fluid. The gastrointestinal tract down to the cecum was filled with bloody material. The stomach, duodenum, small bowel and first half of the cecum were infarcted. The liver weighed 1,600 gm.; its lower border was two fingerbreadths below the costal margin. It was firm in consistency and there was slight fatty infiltration. The spleen weighed 250 gm. and was dark red in color and moderately firm in consistency. Together the kidneys weighed 250 gm. and were coarsely granular. His-

tologically sections of the stomach (Fig. 5) and bowel showed infarction; the liver showed slight increase in periportal fibrous tissue and bile duct proliferation. The spleen showed no significant lesion.

Anatomic diagnoses were as follows: arteriosclerotic aneurysm of the abdominal aorta; mural thrombosis of aorta; arteriosclerosis of aorta, generalized; infarction of stomach, duodenum, small bowel and cecum; pulmonary edema; bronchopneumonia; hypertensive heart disease; and left ventricular hypertrophy.

CASE IV. R. R., a sixty-seven year old Mexican woman, was admitted to the Los Angeles County Hospital on November 16, 1936. She had been seized suddenly with severe, gripping pain in the epigastrium two hours prior to admission. Vomiting occurred soon after the onset of pain and several times thereafter. Vomitus consisted of recently digested food. She was unaware of hypertension but had recurring dyspnea on exertion. Physical examination revealed a well developed woman complaining of pain in her abdomen and choking sensation over the precordium. Her face and hands were cold and clammy. Her temperature was 98°F., pulse 120, respirations 30 and blood pressure 270/150. The heart was enlarged to the axillary line in the fifth interspace; the rhythm was regular. A-2 was accentuated. Murmurs were obscured by grunting noises. There were numerous moist crepitant rales and musical rales at both bases. The abdomen was not distended. There was voluntary and reflex rigidity in the upper portion with marked tenderness. No organs or masses were palpable and peristalsis was normal. Laboratory tests revealed red blood cells, 6,150,000; white blood cells, 26,000; 86 per cent polymorphonuclears. The urine showed a specific gravity of 1.005, albumin 1 plus, trace of sugar and an occasional pus cell, with three to five red blood cells per high power field. Scout film of the abdomen showed scattered intestinal gas, largely colonic. An electrocardiogram showed left ventricular hypertrophy. The chest x-ray showed an enlarged heart and redundant aorta. The left diaphragm was somewhat elevated.

The following day the patient's temperature rose to 102.8°F. rectally. The blood pressure dropped to 110/70; she became restless, her abdomen became silent and she expired.

Autopsy was performed fourteen hours after death. The heart weighed 460 gm., its apex being in the anterior axillary line. There was slight dilatation of the right heart. The left ventricle measured 16 mm. and the right, 4 to 5 mm. The coronary arteries were patent but narrowed by atherosclerotic plaques. The myocardium showed diffuse scarring. The thoracic and abdominal aorta contained mural thrombi. The celiac axis was completely closed by a thrombus which originated as a mural thrombus in the wall of the aorta and extended by continuity into the lumen of the celiac axis. The left lung weighed 450 gm. and the right, 580 gm.; both were somewhat edematous. Along the greater curvature of the stomach, in the area supplied by the short gastric branches of the splenic artery, there was necrosis, gangrenous sloughing and erosions of the mucosa, with marked discoloration. The pyloric end of the stomach and duodenum were normal as was the remainder of the intestinal tract. The liver weighed 1,320 gm. and was deep brown in color with distinct lobular markings. There were no areas of infarction, hemorrhage or necrosis seen. The spleen weighed 60 gm. and was brownish purple in color; its external surface was wrinkled and contracted. There was an increase in the fibrous stroma. The kidneys together weighed 160 gm.; they were granular and contained a few deep U-shaped scars. Histologically the liver showed passive congestion; sections of the spleen showed infarction.

Anatomic diagnoses were as follows: arteriosclerosis, generalized, severe, of aorta; mural thrombi of aorta; thrombosis of celiac axis; infarction of spleen and of stomach with gangrene; pulmonary edema; coronary sclerosis without occlusion; nephrosclerosis, benign; and hypertensive heart disease.

ANATOMIC CONSIDERATIONS

When one considers the abundant vascular supply and excellent anastomoses of the stomach circulation, it is not surprising that infarction occurs so infrequently. All the arteries supplying the stomach freely anastomose with one another. The left gastric artery runs along the lesser curvature to the right and downward and unites with the right gastric artery. The right gastric artery, which takes its origin from the hepatic artery or proximal portion of the gastroduodenal artery, runs along the lesser curvature to the left and gives off branches to the anterior and posterior walls of the stomach. The right gastroepiploic artery runs to the left along the

greater curvature of the stomach and unites with the left gastroepiploic artery. It gives branches to the anterior and posterior walls of the stomach. The left gastroepiploic artery, which arises from the splenic artery, passes to the right along the greater curvature; its branches are like those of the right gastroepiploic artery. The vasa brevia arising from the splenic artery send branches to the fundus.[11] Babkin et al.[12] found that tying all the gastric arteries (esophageal left intact) does not deprive the dog stomach of its arterial circulation. After operation the arterial blood supply is maintained through the multiple anastomoses between the left gastric artery and branches of the phrenic and esophageal arteries. They also noted that with gastric arteries ligated all the surrounding organs (one or both lobes of the liver, spleen, omentum, pancreas and left kidney) participate in the revascularization of the stomach. They state that "because of these anastomotic channels, there is little possibility that the stomach will be deprived altogether of its blood supply unless the de-arterialization is complete or venous flow is impeded."

Somervall[13] has performed arterial ligations of the gastric vessels in nearly 400 cases to relieve hyperacidity and to prevent ulceration after gastroenterostomy in humans. In many instances the procedure employed was ligation of the four main vessels with additional ligation of four of every five of the smaller branches going to the stomach wall. He was careful not to interfere with the venous return from the stomach. In only one case, in which gangrene of the spleen occurred, was there a fatal result. Furthermore it has been well demonstrated that the human stomach can remain viable even when almost completely deprived of its blood supply. This is seen in the operation for carcinoma of the stomach when the stomach is drawn into the chest and anastomosed to the esophagus.[14]

Lipschutz[15] in a study of eighty-three cadavers found that the vascular variations of the celiac axis artery could be classified into four groups. In 75 per cent of cases the celiac axis is the common trunk of origin for the gastric, splenic and hepatic arteries. In 15 per cent of the cases the gastric artery occurs as a separate branch directly from the abdominal aorta cephalic to the origin of the celiac axis, the latter giving rise to the hepatic and splenic arteries. In 6 per cent the gastric and hepatic arteries take origin from the celiac axis; the splenic artery arises as a separate branch from the abdominal aorta. In the fourth group representing 4 per cent of cases the celiac axis is the trunk of origin for the gastric and splenic arteries and the hepatic artery occurs as a separate branch directly from the abdominal aorta. From this it becomes apparent that in at least 75 per cent of individuals the gastric circulation is dependent upon the integrity of the celiac trunk.

EXPERIMENTAL

Bernheim[16] attempted to diminish gastric secretion by devascularization of the stomach. He concluded from experiments in eighteen dogs that short of complete devascularization the stomach of the dog could withstand any degree of diminution of its blood supply whether on the lesser or the greater curvature. When total devascularization was done, it was the greater curvature that became gangrenous, the lesser curvature being unaffected. This latter observation is interesting in view of the anatomic study of Reeves.[17] In seeking an explanation for the great majority of peptic ulcers occurring on the lesser curvature Reeves showed that the arteries in this region are predisposed to thromboses. The plexus of vessels in the submucosa is made up of much smaller and longer arteries without as free anastomoses as in other regions of the stomach. The branches from this plexus run a very tortuous course to enter the mucosa. The resistance offered to the blood stream is constantly greater and, as a result, the blood current is slower as it enters the small arteries of the mucosa. The submucosal plexus of arteries in the first inch of the duodenum is made up of relatively few vessels in comparison with other parts of the duodenum. They are small and do not anastomose freely; they give off branches to the mucosa which simulate the gastric type of spiral artery. The rather limited blood supply and the gastric type artery predispose to thrombosis. Worthy of note is the appearance of the stomach in Cases I and II. (Figs. 1 and 3) The lesser curvature although infarcted is grossly pale when compared with the intensely hemorrhagic state of the remainder of the stomach.

Baronofsky and Wangensteen[18] in their study on dogs and rabbits showed that obstruction of the venous drainage of the stomach abets the ulcer diathesis. Erosions and ulcers are far more readily provoked with histamine in the presence of portal hypertension than when there is no obstruction to venous outflow. They noted that

partial obstruction of the splenic vein increased the weight of the stomach. Layne and Bergh[19] found that sudden acute ligation of the celiac axis or ligation of the four large arteries of the stomach in the dog resulted in death of the animal within six to thirty-six hours. They failed to recognize the importance of ligation of the splenic vein, a procedure performed in each of their dogs. Babkin et al.[12] also found that tying all the gastric arteries and veins in dogs produced necrosis of the stomach in each case. Brenckman[20] examined the devascularized stomach histologically. He states that a month after complete devascularization the gastric mucosa in his dogs had a normal appearance although it seemed to be less vascular than prior to surgery. Soon after operation his dogs could even digest bones seemingly without difficulty. Baronofsky[18] found no infarction after arterial ligation but he was careful not to ligate the venous return. Le Veen[13] noted that arterial devascularization did not result in infarction if the stomach was handled with extreme gentleness. He noted the lack of extensive collateral development as long as four months after arterial ligation and concluded that the effects of such extensive ligation would be permanent.

MacCallum[21] cites a case of celiac axis thrombosis in which there was not the slightest disturbance in the appearance of the abdominal organs. In his case there was dilatation of the pancreaticoduodenal artery which transmitted the whole blood supply to the stomach.

COMMENTS

It seems well established from experimental work in animals and surgery in humans that dearterialization of the stomach, without disturbance of the integrity of the venous return, does not result in significant pathologic alteration in the gastric wall. Although arterial ligation of the stomach has not been detrimental in man, it is conceivable that were congestive failure or other interference of the venous circulation to ensue at some future date infarction would occur. Ritterhaus[22] has reported a case in which the superior mesenteric artery was occluded but infarction of the bowel did not take place until heart failure supervened. Celiac artery occlusion may occur in the human without producing infarction of the stomach. It is possible that in some of these patients there is an anomalous arrangement of the celiac axis, so that the stomach is supplied via either the splenic, hepatic or gastric artery, which in these cases takes its origin directly from the aorta.

Case I demonstrates well the production of gastric infarction by arterial obstruction and impediment to venous flow. This patient had congestive heart failure and an embolism to the celiac artery; the necessary features for infarction, according to the experimental work, were present. Failure of the right heart is tantamount to ligation of the entire venous return of the stomach including any anastomotic venous channels which may exist. Case III presents a similar although less clear-cut situation. This patient had hypertensive heart disease (heart weight 600 gm.) with passive congestion in the liver and spleen. There were severe atherosclerotic changes in the aorta, with a large arteriosclerotic aneurysm just below the origin of the celiac artery. The manner in which the aneurysm produced obstruction to the blood flow through the celiac trunk is not clear. Johnson and Baggenstoss[23] found that the extent of arterial occlusion necessary to produce intestinal infarction was less than for venous obstruction. In Case IV partial gastric infarction resulted from celiac axis occlusion in a patient with hypertensive heart disease. The situation in these cases is comparable to that obtaining in mesenteric occlusion. In the cases reported by Johnson and Baggenstoss[22] bowel infarction occurred in all the cases with both mesenteric artery and vein occlusion. In 75 per cent of sixty cases mesenteric arterial occlusion resulted in partial or complete bowel infarction depending upon the size of the vessel involved.

That venous obstruction can produce complete gastric infarction is seen in Case II in which there was severe cor pulmonale. The right ventricle measured 6 mm. in thickness (in spite of dilatation) as compared with a left ventricle of 13 mm. It is of great interest that the entire small and large bowel were also infarcted. Although there was severe atherosclerotic change in the aorta at the site of origin of the visceral vessels, no gross obstruction was found. It would seem unnecessary to postulate an arterial ischemic component in view of the already mentioned fact that infarction can occur secondary to venous obstruction. Partial infarctions of the stomach have been described due to venous occlusion alone. Circumscribed infarctions have occurred with portal vein thrombosis, subacute portal vein thrombophlebitis and thrombosis of the coronary vein. Venous occlusion may result

in infarction of various organs such as the spleen,[24] kidney,[25] brain,[26,27] breast[28] and striated muscle.[29] Haimovici[30] has reviewed twenty-seven cases of gangrene of an extremity due to venous obstruction without arterial occlusion. He suggests that the mechanism is a circulatory arrest caused by complete blockage of the venous return due to extensive venous occlusion. Infarction of the bowel was present in fifty-two of ninety-nine cases of mesenteric venous occlusion reported by Johnson and Baggenstoss.[31]

SUMMARY

Experimental data gathered from the literature seem to indicate that if infarction of the stomach is to be produced both arterial ligation and venous impediment are requisite. Almost complete dearterialization of the stomach in animals and humans does not result in vascular lesions. Interference with venous flow, as seen in portal vein obstruction and coronary vein thrombosis, may result in partial infarction of the stomach.

The hitherto unknown entity of complete gastric infarction is presented, with a report of three cases. A case of partial gastric infarction is included. One of the cases of total infarction was associated with complete infarction of the alimentary tract below the diaphragm. These cases suggest that the mechanisms producing infarction of the stomach are not different from those producing infarction in other organs. Arterial, venous or a combination of arterial and venous occlusion can result in gastric infarction. Infarctions of the stomach were all hemorrhagic and when complete were associated with small or large bowel infarction or both.

Acknowledgment: I wish to express my gratitude to Doctors E. M. Butt, W. E. Macpherson, A. E. Hirst, E. Phillips and M. Reinberg for their encouragement and suggestions in the preparation of this paper, and to Lloyd Matlovsky for the preparation of the photographs.

REFERENCES

1. Mallory, T. B. Personal communication.
2. Pack, G. T. Personal communication.
3. Popper, H. Personal communication.
4. Rich, A. R. Personal communication.
5. Callender, G. R. Personal communication.
6. Broders, A. C. Personal communication.
7. Baumann, A. W. Hemorrhagic Infarcts of the Stomach Produced through Embolic Occlusion of Arterial Vessels of the Stomach. Thesis. Munich, 1909. C. Wolf & Sohn.
8. Manfrini, P. and Gerundini, G. Infarcto hemorragico e perforazione dello stomaco in un bambino, come complicanza di ustioni. *Pediatrica*, 47: 910–927, 1939.
9. Platt, W. R. Thrombosis of gastric vein with spontaneous rupture of the stomach. *Arch. Path.*, 40: 403–404, 1945.
10. Halbron, P. Delarne, J., Lenormand, J. and Raymond, M. Splenomegalie premonitoire d'une thrombo-phlebite subaigue du systeme porte et hemorragies gastriques par infarctus de l'estomac. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 54: 1147–1152, 1938.
11. Spalteholz, W. Hand-atlas of Human Anatomy, vol. II. Philadelphia, 1923. J. B. Lippincott Co.
12. Babkin, B. P., Armour, J. A. and Webster, D. R. Restoration of the functional capacity of the stomach when deprived of its main arterial blood supply. *Canad. M. A. J.*, 48: 1–10, 1943.
13. Somervall, T. H. Physiological gastrectomy. *Brit. J. Surg.*, 33: 146–152, 1945.
14. LeVeen, H. H. Effect of surgical interruption of the gastric blood flow upon gastric secretion and the prevention of experimental peptic ulcers. *Surg., Gynec. & Obst.*, 86: 164–168, 1948.
15. Lipschutz, B. A composite study of the coeliac axis artery. *Ann. Surg.*, 65: 159, 1917.
16. Bernheim, B. M. Partial and total devascularization of the stomach. *Ann. Surg.*, 96: 179–183, 1932.
17. Reeves, T. B. A study of the arteries supplying the stomach and duodenum and their relation to ulcer. *Surg., Gynec. & Obst.*, 30: 374, 1920.
18. Baronofsky, I. and Wangensteen, O. H. Obstruction of the splenic vein increases weight of stomach and predisposes to peptic ulcer. *Proc. Soc. Exper. Biol. & Med.*, 59: 234–238, 1945.
19. Layne, J. A. and Bergh, G. S. The effect of ligation of arteries of the stomach upon acid gastric secretion and upon endoscopic appearance of the gastric mucosa in the dog. *Surgery*, 13: 136–144, 1943.
20. Brenckmann, E. Quoted by Babkin et al.[12]
21. MacCallum, W. G. Textbook of Pathology. Philadelphia, 1940. W. B. Saunders Co.
22. Ritterhaus. Quoted by Johnson and Baggenstoss.[23]
23. Johnson, C. C. and Baggenstoss, A. H. Mesenteric vascular occlusion. II. Study of 60 cases of occlusion of arteries. *Proc. Staff Meet., Mayo Clin.*, 24: 649–656, 1949.
24. Geiser, P. and Studer, A. Quoted by Haimovici.[30]
25. Melick, W. F. and Vitt, A. E. Quoted by Haimovici.[30]
26. Marbury, O. and Casemajor, L. Quoted by Haimovici.[30]
27. Martin, J. P. et al. Quoted by Haimovici.[30]
28. Flood, E. P. et al. Quoted by Haimovici.[30]
29. Wertheimer, P. et al. Quoted by Haimovici.[30]
30. Haimovici, H. Gangrene of the extremities of venous origin. *Circulation*, 1: 225–240, 1950.
31. Johnson, C. C. and Baggenstoss, A. H. Mesenteric vascular occlusion. I. Study of 99 cases of occlusion of veins. *Proc. Staff Meet., Mayo Clin.*, 24: 628–636, 1949.

Ball Thrombus of the Right Auricle*

ROBERT S. RADDING, M.D.

Houston, Texas

ONE of the most interesting, albeit one of the rarest, complications of heart disease is the formation of globular or ball thrombi within the chambers of the heart. Through the years attempts have been made to correlate the clinical and pathologic findings of the condition so as to make diagnosis possible prior to examination at autopsy. It is the purpose of this study to review the past literature, establish criteria for diagnosis and, finally, to add to the literature an unusual case of ball thrombus of the right auricle.

The pathologic condition now known as ball thrombus was first reported by Wood in 1814.[1] He described the case of a fifteen year old girl whose chief complaint was fainting spells which occurred three or four times a day. Clinical findings of mitral stenosis were substantiated by the postmortem examination but in addition a spherical thrombus was observed within the left auricular chamber. This thrombus measured 1½ inches in diameter and apparently occluded the mitral orifice.

A succession of case reports of similar findings followed until 1896 when Welch laid down three criteria for postmortem diagnosis. Up to that time fourteen authenticated cases had been reported including those of Ogle,[2] Legg,[3] von Recklinghausen,[4] Hertz[5] and Osler.[6] The criteria of Welch[7] require that there be: "(1) entire absence of attachment and consequent mobility, (2) imprisonment in consequence of excess in the diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it and (3) such consistence and shape that the thrombus must not of necessity lodge as an embolus in this passage."

The present review of published cases was prepared with these criteria in mind and consequently several cases of globular thrombi attached by a pedicle have been eliminated. Cases presented by Garvin[8] and Spain,[9] for example, have not been included in the total series as both report attachment to the auricular wall by means of a pedicle.

In 1913 Hewitt[10] reviewed the early literature in this subject. He then added his own case which brought the total to twenty-two authentic cases, including those presented by Osler,[11] Ziemssen,[12] Schmorl,[19] Redtenbacher,[13] Rosenbach,[14] Krumbholz,[19] Tauber,[15] Söhlein,[19] Szász[16] and French.[17] Mathewson and Rutherford[18] described their case in 1920. In 1924 the early literature was again reviewed by Abramson[19] who added one more case of left auricular ball thrombus. Since 1924 several reports have appeared describing ball thrombi but some have been omitted here because of attachment by a pedicle or fibrinous adhesions. Three cases were subsequently described by Cleland[20] in 1936 but these are omitted because no pathologic substantiation was included in the report. Schwartz and Biloon[21] reported a case in 1931 but no mention of attachments (or the lack of such) was made and therefore this case is not included.

Potter[22] observed a case of ball thrombus at autopsy in 1926 and in 1928 Covey, Crook and Rogers[23] described a case of ball thrombus which was diagnosed prior to death. This latter case is significant because the clinical diagnosis of the condition had never been made correctly up to that time. (In 1896 by Bozzolo[24] and in 1909 by Battistini[25] (two cases) clinical diagnosis was made but in all three cases the intracardiac thromboses were attached to the auricular wall.) Aronstein and Neuman[26] observed a case of ball thrombus in 1939.

In reviewing the findings in a large group of patients with rheumatic heart disease Garvin[8] found two authentic cases of ball thrombus and a third case of a thrombus attached by a pedicle. In 1945 Wright, Flynn and Druet[27] reported the first observation of a ball thrombus of the right auricle and in this instance the diagnosis was made prior to death. The present case is also a ball thrombus of the right auricle. A brief tabular description of each authentic case is given in Table I.

* From the Department of Medicine, Indianapolis General Hospital, Indianapolis, Ind.

TABLE I

SUMMARY OF TWENTY-NINE CASES OF BALL THROMBUS

Case and Author	Sex	Age	Clinical Findings	Pathologic Condition
1. Wood (1814)	F	15	Fainting spells, sudden death	Right auricle and ventricle enlarged; mitral stenosis; thrombus, 1½ in.
2. Ogle (1863)	F	43	Dyspnea	Mitral stenosis, thrombus
3. Legg (1878)	M	22	Dead on arrival	Thrombus (15 by 30 mm.); thickened right ventricle; mitral stenosis
4. Legg (1878)	F	43	No clinical data	Thickened right ventricle; mitral stenosis; thrombus 1½ in. in diameter
5. v. Recklinghausen (1883)	..	..	None given	Mitral stenosis; thrombus of walnut size
6. v. Recklinghausen (1883)	..	..	None given	Mitral stenosis
7. Hertz (1885)	M	23	Palpitation, dyspnea, edema, cyanosis	Mitral stenosis; thrombus 2.5 cm.
8. Hertz (1885)	..	39	Generalized edema	Thrombus 4 cm.; mitral stenosis; left ventricle hypertrophied
9. Osler (1890)	F	35	Dyspnea 20 years, hemiplegia with aphasia	Thrombus 1.5 by 2.5 cm.; mitral stenosis; aortic valves thickened
10. Ziemssen (1890)	..	..	.....	Mitral stenosis; thrombus of walnut size
11. Schmorl (1892)	..	..	.....	Mitral stenosis; thrombus of hen's egg size
12. Redtenbacher (1892)	F	46	Edema of feet	Cardiac enlargement; mitral stenosis; thrombus 3.5 cm.
13. Rosenbach (1893)	..	..	Presystolic and diastolic murmur	Mitral stenosis; nut-sized ball thrombus
14. Krumbholz (1893)	F	41	Dyspnea and palpitation, severe cyanosis, cold extremities and pedal edema	Hen's egg thrombus; mitral stenosis
15. Tauber (1896)	M	28	Cyanosis, edema, irregular rhythm, hepatomegaly	Mitral stenosis; thrombus 3.5 cm.
16. Osler (1897)	F	20	Edema of legs, "facies luetica," presystolic murmur	Thrombus 3 cm.; mitral stenosis
17. Söhlein (1896)	F	47	Severe cyanosis, rapid pulse, facial paralysis	Mitral stenosis; thrombus 3.2 by 2.2 by 2.2 cm.
18. Szász (1908)	M	16	Pneumonia, dyspnea, hemoptysis	Mitral stenosis; thrombus of hazel nut size
19. French (1912)	F	44	Dyspnea, swelling of legs	Mitral stenosis; thrombus of eyeball size
20. Hewitt (1916)	F	38	Dyspnea, palpitation, edema, left heart enlarged	Mitral stenosis; thrombus 3.5 cm.
21. Mathewson and Rutherford (1920)	F	49	Dyspnea, deep cyanosis	Thrombus of walnut size; mitral stenosis
22. Abramson (1924)	F	43	Cardiac pain, cold extremities	Mitral stenosis; thrombus 3.5 cm.
23. Potter (1926)	F	53	Coldness in extremities	Mitral stenosis; thrombus 5.5 by 4.5 by 4 cm.
24. Covey, Crook and Rogers (1928)	F	55	Diminished peripheral circulation, diagnosed before death	Thrombus 3 cm.; mitral stenosis
25. Aronstein and Neuman (1939)	F	43	Marked cyanosis and dyspnea	Mitral stenosis; thrombus 3.5 cm.
26. Garvin (1941)	F	48	Ischemia, necrosis of right foot and attacks of syncope	Mitral and tricuspid stenosis; thrombus 3 cm.
27. Garvin (1941)	F	86	Ischemia, necrosis of right foot, pulseless lower extremities	Mitral stenosis; thrombus 2.2 cm.; coronary arteriosclerosis
28. Wright, Flynn and Druet (1944)	M	47	Engorgement of neck veins, air hunger	Mitral stenosis; ball thrombus of right auricle
29. Author s case (1951)	F	22	Fever, cough, air hunger, sudden death	Acute bacterial endocarditis

Note: In all but Case 29 there was associated rheumatic heart disease and mitral stenosis. The ball thrombus was located in the left auricle in all cases except Cases 19, 28 and 29.

CASE REPORT

D. D., a twenty-two year old colored housewife, was admitted on July 11, 1949, with the complaint of pain in the chest. The onset of symptoms was four weeks previously with fever, weakness, cough and chest pain. Temporary improvement was effected at that time with the administration of "two shots" of penicillin. The patient continued to be weak and had a chronic productive cough; anorexia developed. One week prior to admission pain developed in the lower left chest, having previously involved the right lateral chest wall. The symptoms were gradually progressive. History by systems was negative except for an episode of syncope on the morning of admission, exertional dyspnea associated with cough and expectoration of clear, odorless sputum, and occasional postprandial vomiting without nausea.

Physical examination showed a poorly nourished patient who was extremely weak and appeared chronically ill. The blood pressure was 102/66, the pulse rate 100. The eyes, ears, nose and throat were essentially normal except for a fetid odor to the breath. The skin was warm and moist. The chest revealed bilateral restriction of respiration with decreased resonance below the level of the fourth thoracic vertebra on the right posteriorly and flatness to percussion between the ninth and twelfth thoracic vertebrae on the right posteriorly. Bronchial breathing was present throughout both lung fields with decreased breath sounds over the area described heretofore. Coarse breath sounds were heard over the right base except for absence of breath sounds in extreme basilar portions. Examination of the heart was essentially negative except for a harsh sound heard over the sternum, interpreted as a friction rub which also radiated to the back. The remainder of the examination was essentially normal except for profuse leukorrhea.

Radiographic studies on admission revealed evidence of pneumonitis of the left lobe of the lung with questionable multiloculated abscesses in the right middle lobe. On July 19th roentgenogram showed "multiple areas of cavitation throughout both lung fields with some infiltrative changes." On July 29th there was a definite decrease in the previously described density in the lung. Another density was observed, however, in the middle third of the left lung field and this had not been present on previous examination. On August 12th there was slight cardiac enlargement with a pyramidal infiltrate in the middle left lung field and several thick-walled cysts.

The laboratory data were as follows: Urinalysis was repeatedly negative. The hemoglobin was 9.5 gm. per cent, the white blood count was 34,600 with 60 polymorphonuclears, 19 band forms, 6 eosinophils, 7 lymphocytes and 1 monocyte sedimentation rate was 31. Kline and Kahn tests were negative. Routine agglutinations were also negative. Vaginal smear was positive for intracellular gram-negative diplococci. The antistreptolysin titer was 50 units. Sputum revealed alpha hemolytic streptococcus; yeast cells were present in the second examination. Blood cultures were negative throughout the course in the hospital.

On penicillin therapy the patient improved slightly but began to have spiking fevers daily. Therapy was augmented with sulfadiazine, salicylates and, for a short period, aureomycin. The course was consistently poor. The findings on chest examination were constantly changing. The precordial friction rub diminished, probably due to an increase in the amount of fluid within the sac. The electrocardiogram was consistent with pericarditis. Blood transfusions brought about no improvement in the anemia.

On August 11, 1949, a grade 1 systolic murmur was heard over the tricuspid area. Suddenly on August 19, 1949, the patient complained of substernal pain and showed extreme air hunger. The patient was very apprehensive and in acute respiratory distress. Oxygen was employed. Within ten minutes the patient had convulsive movements with gasping respirations and expired.

At postmortem examination upon opening the pericardial sac about 500 cc. of pericardial fluid were present. The anterior surface arteries of the heart showed two fibrous plaques not more than 1 cm. in diameter. Coronary examination showed no abnormalities. The heart weighed 300 gm. The right ventricle appeared moderately dilated and the pulmonary valves were normal. An organized globular thrombus about 3 cm. in diameter was found lying free within the right auricle. There were no attachments.

The tricuspid valves showed the presence of two relatively normal leaflets. The third leaflet was absent or densely adherent to the ventricular wall. The surface of the tricuspid valve was covered with a moderately large, irregular, friable mass which was gray-white in color. The left auricle was normal in size. The mitral valve

showed a mild degree of scarring along its extreme margin 1.5 cm. in length. The aortic valve was normal.

Microscopically, sections of the thrombus showed a homogeneous pink-staining material which was apparently thrombus with a moderate number of leukocytes present along the edges. These leukocytes included polymorphonuclears, eosinophils, monocytes and lymphocytes.

The anatomic diagnosis was as follows: ball thrombus of the right auricle; acute vegetative endocarditis of tricuspid valve due to Friedländers' bacillus (cultured from pulmonary lesions).

COMMENTS

A total of twenty-nine cases of ball thrombus conforming to Welch's criteria are summarized in Table 1.

The sex of the patient was noted in twenty-three cases, and in eighteen or 78 per cent the patient was female. The average age of the twenty-four cases so noted was 39.3 years. Of the twenty-nine ball thrombi herein presented twenty-six occurred in the left auricle; the right ventricle was involved in one case and on two occasions the right auricle was the site of thrombosis. In all except the present case the formation of a ball thrombus was associated with rheumatic heart disease and mitral stenosis. In this last case the ball thrombus was associated with acute bacterial endocarditis due to Friedländers' bacillus.

All instances of ball thrombi so far recorded have shown varying degrees of cardiac disease, usually of a severe nature; in most, dyspnea, cyanosis and edema have been the rule. In those cases in which the diagnosis had been suspected prior to death peripheral vascular ischemia was the rule except in the case of right auricular thrombus presented by Wright et al.[27] In that instance the diagnosis was based on dusky cyanosis of the face and neck, enlargement of the veins of the neck, air hunger type of dyspnea, enlargement of the right side of heart, murmurs of tricuspid insufficiency and venous engorgement of the liver with a rapidly changing roentgenogram and physical findings. In the present case these signs were not present, with the exception of a tricuspid murmur and dyspnea of the air hunger type during the terminal episode.

Apparently the cardinal sign in ball thrombus of the *left* auricle is decreased peripheral circulation with ischemia, particularly in the lower extremities, associated invariably with rheumatic heart disease and mitral stenosis, usually in a female patient. Ball thrombus of the *right* auricle should be suspected in patients who demonstrate a tricuspid murmur, air hunger and rapidly changing clinical and radiographic findings associated with physical signs of right ventricular failure.

It is interesting to note that the present case was not associated with either mitral stenosis or rheumatic heart disease, but rather with acute bacterial endocarditis. In all probability vegetations were engrafted on the tricuspid valve and in consequence one of the valve leaflets was destroyed and subsequently broke off. This fragment in turn became the nucleus for the formation of a ball thrombus. No organisms were obtained in repeated blood cultures. The lungs showed numerous abscesses which grew out Klebsiella pneumoniae on culture.

Many cases of occluding thrombi of the heart have been omitted because the criteria of Welch[7] have not been fulfilled. However, many of these have demonstrated the classical clinical picture heretofore described. No actual differentiation can be made prior to death as to the presence or absence of any attachment to the endocardium. It might be well, therefore, to include at some future date all cases of occluding thrombi of the heart for the sake of defining diagnostic symptoms and signs.

CONCLUSIONS

1. A case of ball thrombus of the right auricle is presented, associated with acute bacterial endocarditis due to Friedländers' bacillus. A search of the literature reveals that this is the second instance of ball thrombus of the right auricle to be reported.

2. In a review of the literature twenty-eight authenticated instances of ball thrombus of the heart have been found.

3. Analysis of statistics reveals that this condition occurs predominantly in female patients who, in all except one case, had associated rheumatic heart disease or mitral stenosis.

4. The diagnosis of intracardiac thrombosis of the left heart is to be suspected when progressive peripheral ischemia, particularly of the lower extremities, develops in patients with mitral disease. Involvement of the right heart should be suspected when the clinical aspects of right ventricular failure are complicated by

dusky cyanosis, air hunger and a rapidly changing clinical picture.

REFERENCES

1. Wood, W. A letter enclosing the history and dissection of a case in which a foreign body was found within the heart. *Edinburgh M. & S. J.*, 10: 50, 1814.
2. Ogle, J. W. Fibrinous concretion of a globular form and of about one inch in diameter, lying loose within the left auricle of the heart. *Tr. Path. Soc. London*, 14: 127, 1863.
3. Legg, J. W. Two cases of loose balls of fibrin in the left auricle with mitral stenosis. *Tr. Path. Soc. London*, 29: 49, 1878.
4. Von Recklinghausen, F. D. Handbuch d. allegem. Path. d. Kreiselaufs u. d. Ernährung. Stuttgart, 1883.
5. Hertz, W. Ueber ältere Thrombenbildungen im Herzen. *Deutsches Arch. f. klin. Med.*, 37: 74, 1885.
6. Osler, W. Rare forms of cardiac thrombi. *Johns Hopkins Hosp. Rep.*, 2: 745, 1890.
7. Welch, W. Thrombosis. In: Allbutt's System of Medicine. Vol. 6, p. 720. London, 1899. Macmillan & Co.
8. Garvin, C. F. Ball thrombi in the heart. *Am. Heart J.*, 21: 371, 1941.
9. Spain, D. M. Ball thrombus in the heart. *Ann. Int. Med.*, 19: 144, 1943.
10. Hewitt, J. H. Free thrombi and ball thrombus in the heart. *Johns Hopkins Hosp. Rep.*, 17: 1, 1916.
11. Osler, W. Mitral stenosis—sudden death—ball thrombi in the left auricle. *Montreal M. J.*, 25: 729, 1897.
12. Ziemssen, V. Zur Pathologie und Diagnose der Gestielten und Kugelthrombus des Herzens. *Cong. f. inn. Med.*, 9: 281, 1890.
13. Redtenbacher, L. Ein Fall von Combination eines Gestielten und eines Kugelthrombus im linken Vorhof. *Wien. klin. Wchnschr.*, 5: 688, 1892.
14. Rosenbach, O. Die Krankheiten des Herzens und ihre Behandlung, p. 180, 1893.
15. Tauber, E. Ein Fall von Kugelthrombus. *Jahrb. d. Wien. K. K. Kranken-Anstalten*, 5: 345, 1896.
16. Szász, B. Ein Kugelthrombus im linken Vorhof. *Prest. med. Chir.*, 44: 854, 1908.
17. French, H. Ante-mortem clot in the right ventricle. *Guy's Hosp. Rep.*, 66: 357, 1912.
18. Mathewson, G. D. and Rutherford, A. A case of cardiac ball-thrombus. *Lancet*, 2: 745, 1920.
19. Abraham, J. L. Ball thrombus of the heart. *Ann. Clin. Med.*, 3: 327, 1924.
20. Cleland, J. B. Ante mortem clots in the chambers of the heart. *M. J. Australia*, 2: 56, 1936.
21. Schwartz, S. B. and Biloon, S. Clinical signs of occluding thrombi of the left auricle. *Am. Heart J.*, 7: 84, 1931–1932.
22. Potter, E. B. A new case of free ball thrombus associated with mitral stenosis. *Ann. Clin. Med.*, 4: 736, 1926.
23. Covey, G. W., Crook, R. and Rogers, F. L. Ball thrombus of the left auricle. *Am. J. M. Sc.*, 175: 60, 1928.
24. Bozzolo, C. Su di un Caso do Trombosi del Cuore Diagnostica in Vita. *Riforma med.*, 1: 98, 1896.
25. Battistini, F. Due casi di trombosi dell orrechietta sinistra, diagnostica in vita. *Gior. d. r. Accad. di med. di Torino*, 72: 313, 1908–1909.
26. Aronstein, C. and Neuman, L. Ball thrombus of the heart. *Arch. Path.*, 27: 907, 1939.
27. Wright, I. S., Flynn, J. E. and Druet, K. L. Ball thrombus in the right auricle of the heart, with a description of the symptoms produced. *Am. Hear. J.*, 27: 858, 1944.

Disseminated Visceral Torulosis without Nervous System Involvement*

With Clinical Appearance of Granulocytic Leukemia

SAMUEL ZELMAN, M.D., ROBERT H. O'NEIL, M.D. *and* ALFRED PLAUT, M.D.
Topeka, Kansas

A TWENTY-FIVE year old white male college student was well until early February, 1949, when he noticed increasing fatigue, aching in the muscles of his right leg and a daily temperature elevation. These symptoms continued for three weeks before he consulted a physician. At this time a markedly elevated leukocyte count was found and the patient was referred to the Veterans Administration Hospital at Des Moines, Iowa, where he was admitted March 29th. The initial physical examination was negative except for an enlarged spleen barely palpable on deep inspiration. The initial erythrocyte count was 3,420,000 per cu. mm. with 10 gm. per cent hemoglobin. The leukocytes numbered 319,000 per cu. mm., one-half of which were segmented granulocytes and the remainder chiefly myelocytes with a few blast forms. Thrombocytes were reported as normal in number. Bone marrow smear on April 1st showed granulocytic hyperplasia, with myelocytes predominating over segmented forms. A few blast forms were seen, with an occasional mitotic figure. Urinalysis revealed four plus albumin, occasional granular casts, two to four red cells and an occasional leukocyte per high power field. A subsequent urinalysis showed a slight trace of albumin but was otherwise normal. Basal metabolic rates on two occasions were plus 49 and plus 27 per cent.

Urethane was administered in dosage of 1 gm. four times daily from April 8th to 20th. During this therapy the leukocyte count dropped gradually to 150,000 of which 67 per cent were mature and 29 per cent immature granulocytes. The latter were myelocytes except for a few blast forms. The spleen was irradiated April 22nd, 25th and 26th, with a total dose of 300 r units. An abrupt drop in the leukocyte count to 24,000 (90 per cent segmented and 10 per cent myelocytes) caused the irradiation therapy to be discontinued.

To be nearer his home the patient was transferred May 16th to Winter Veterans Administration Hospital. The discharge diagnosis of chronic myelogenous leukemia was made. At this time his symptoms were marked general fatigability and soreness in the calves of both legs. He was pale, asthenic and appeared chronically ill. The edge of a firm, smooth, tender spleen was palpated 12 cm. below the left costal margin. A smooth, non-tender liver edge was palpable 2 cm. below the right costal margin. The inguinal lymph nodes were enlarged up to 2 cm. in diameter, discrete and slightly tender. There was moderate tenderness of the calf muscles. The great and small saphenous veins were cord-like and tender bilaterally. Urinalysis and serologic tests for syphilis were negative. The corrected sedimentation rate was 25 mm. per hour by the Wintrobe method. The erythrocyte count was 3,300,000 per cu. mm. with 12.3 gm. per cent hemoglobin. The leukocyte count was 110,000 per cu. mm. with 68 per cent granulocytes (26 per cent segmented and 42 per cent immature cells), 31 per cent lymphocytes and 1 per cent eosinophils. In retrospect, the lymphocytes reported initially are believed to have included micromyeloblasts. The thrombocyte count was 190,000 per cu. mm. Subsequent blood counts are charted in Figure 1. Sternal marrow smears May 23rd and August 30th (Fig. 2) revealed a hyperplastic marrow with markedly increased myelopoiesis. Seg-

* From the Medical Service and Pathology Department of Winter Veterans Administration Hospital. Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

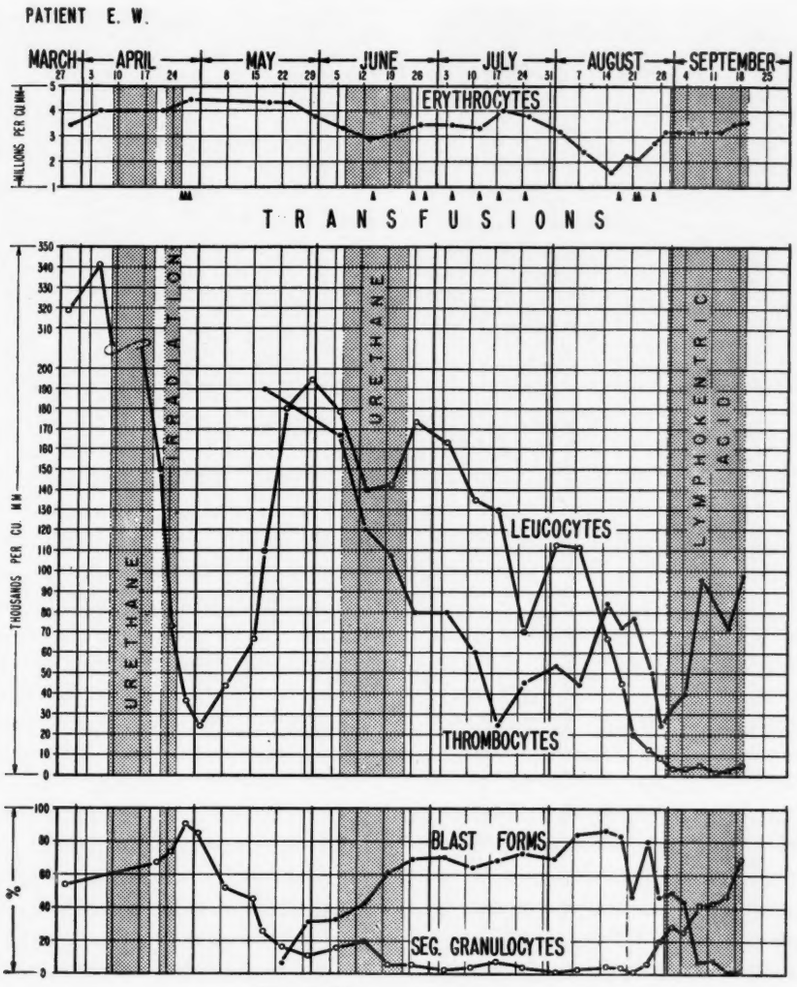
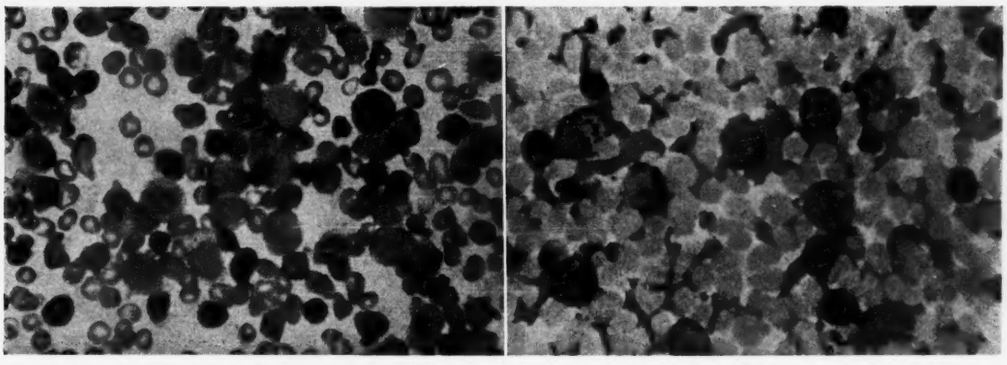


FIG. 1. Hematologic course.



2 3

FIG. 2. Smear of sternal marrow aspirate during life showing hyperplastic myelopoiesis with abundance of blast forms.

FIG. 3. Peroxidase stain of bone marrow aspirate.

FIG. 4. Diffuse and finely nodular cryptococcosis of lung.

mented granulocytes and myeloblasts were present in abundance but intermediate forms were relatively few. The myeloblasts of blood and bone marrow showed peroxidase-staining granules. (Fig. 3.) The blood uric acid was 6.6 mg. per cent. Serum albumin was 3.7 gm. and globulin 2.8 gm. per cent. The initial chest x-ray was negative.

During four months of hospitalization the patient's condition steadily deteriorated. Bilateral thrombophlebitis of the lower extremities was present continuously with frequent exacerbations. There were daily spiking temperature elevations to between 100° and 104°F. However, the patient remained relatively comfortable until the end of his second month in the hospital when right-sided pleural effusion developed. The initial thoracentesis revealed a fluid of specific gravity 1.017, containing 5,700 erythrocytes and 2,000 granulocytes per cu. mm. Many blast forms were noted, a few of which showed mitosis. Smear and culture of this fluid were bacteriologically negative. Repeated thoracenteses were necessary subsequently to relieve dyspnea. Early in September pleural effusion appeared also in the left chest. The fluids at first were straw-colored, later blood-tinged and pre-terminally chylous in appearance. The spleen enlarged gradually until at the end of the sixth hospital week its edge was palpable 18 cm. below the left costal margin. No change in size was then noted until the last thirty days of life when the spleen decreased progressively in size until finally it was no longer palpable. A moderate degree of ascites appeared pre-terminally.

Procaine penicillin G, 300,000 units daily, was administered May 25th to August 23rd and aureomycin 1 gm. daily July 30th to August 10th. Urethane was administered from June 7th to 24th in dosage of 5 gr. three times daily. This was discontinued because of an alarming drop in the thrombocyte count to 80,000 per cu. mm. A low point of 24,000 was recorded on August 30th. On August 17th petechiae appeared on the abdomen, ankles and flexor surfaces of the elbows. A crude lymphokentric acid preparation was administered from August 31st until death. Weakness and weight loss, which had gradually increased from the onset of the illness, became extreme pre-terminally. Dyspnea was no longer adequately relieved by removal of pleural fluid and oxygen therapy was required. A hacking cough, loose stools and decubitus ulcers appeared. The patient died in respiratory failure on September 23rd.

Autopsy was performed two hours after death. The extremely emaciated body weighed only 115 pounds (52 kg.) in spite of the large size (6 feet, 2 inches; 188 cm.). Numbers of small, partly confluent, non-protruding bloody spots were scattered over the anterior surface of the trunk. The subcutaneous fat and the preperi-cardial fat were very thin, brownish and highly edematous. The retroperitoneal tissues, especially in the pelvis, the peritoneum itself, the omentum and the mesentery were highly edematous, glassy and whitish. The abdomen contained 1,000 cc. of thin, milky, odorless fluid. The left pleural cavity contained 1,500 cc. of turbid pink fluid with some fibrin-like flakes. The right pleural cavity contained 2,000 cc. of similar fluid. There were extensive pleural adhesions on both sides.

The pleural surfaces were widely covered with fibrin. Numerous lentil-sized, round, yellow, flat elevations were noted in the left interlobar space. The lower lobe of the left lung was large, firm, heavy and inelastic. Its cut surfaces were homogeneously dull purple with innumerable, small, yellow and gray dots and dashes, resembling a recently disseminated tuberculosis. (Fig. 4.) Dull, strawberry-colored, frothy fluid was scraped from the cut surfaces. The upper lobe and the right lung were less involved. Several intrathoracic lymph nodes contained numerous yellow-gray, confluent, cheesy areas. After fixation the larger part of the cut surfaces appeared yellow; the small single foci had become indistinct except for the ones in the small areas of relatively unaffected lung tissue.

The spleen was 20 cm. long and weighed 670 gm. Its upper half was situated under the costal arch. It was adherent laterally to the parietal peritoneum. The capsule was smooth, the splenic substance was homogeneously dark red, inelastic and practically without markings.

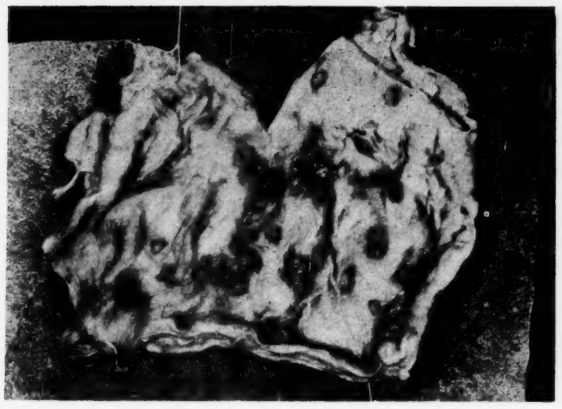


FIG. 5. Necrotic foci of cryptococcosis in colon.

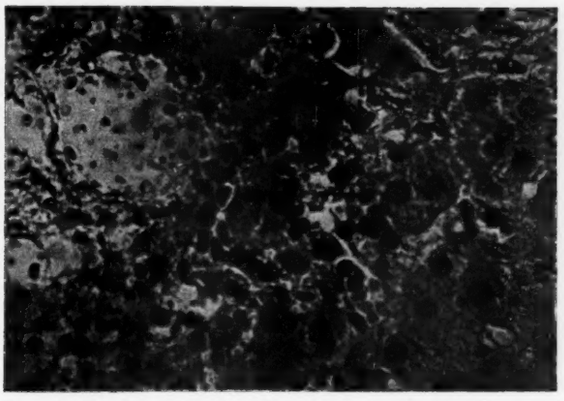


FIG. 6. Section of adrenal cortex, showing a focus of cryptococcic invasion containing whole organisms and breakdown products, surrounded by necrosis.

The liver (1,530 gm.) was not remarkable. The markings of the cut surfaces were indistinct and no focal lesions were found. The adrenal glands and the pancreas were not remarkable.

The cecum and ascending colon were very wide, their mucosa highly edematous, glassy, greenish gray, with numerous small, irregularly outlined, pale red and yellowish, partly ulcerated spots. (Fig. 5.) Transverse, narrow, shallow, dirty yellowish ulcerations were found in the first part of the ascending colon and in part of the transverse colon.

A few discrete, small, gray and yellow dots were seen on the surface of the right kidney, and in an area about 1.5 cm. diameter the surface was irregularly granular and dark reddish. On the cut surfaces the cortex appeared broad and dull strawberry-colored; it was sharply separated from the dark red pyramids.

There were no important gross findings in the meninges and the brain. The leptomeninges were slightly hyperemic, the amount of cerebrospinal fluid was perhaps slightly increased and the third ventricle appeared slightly wide. The brain, on slicing after fixation, did not show any lesions.

Microscopically, the organs gave the characteristic picture of cryptococcosis, with large masses of organisms and little inflammatory reaction. Corresponding to the gross aspects the severest lesions were found in the lungs, the colon and some lymph nodes. The ratio between the number of organisms and the size of the areas occupied by necrosis showed much variation. Inflammatory cells were found at a few points only, notably in the intestine, and there they may have represented reaction to secondary infection. Some lymph nodes were almost entirely replaced by masses of cryptococci and necrosis, some were less involved and others were fairly intact. Occasional small foci were found in the pancreas, the adrenal glands (Fig. 6), the myocardium and the connective tissue from various regions. In the prostate parasites were found almost only in the lumina of the glands.

The large size of the spleen was caused by hyperplasia of the pulp, together with some stasis. The very small follicles and the thin trabeculas appeared wide apart. There were only occasional cells of hemocytoblast type. Neither cryptococci, necrosis nor leukemic change was found in the spleen. The liver appeared practically normal. There was one small granuloma with a few indistinct cryptococci. The liver sinusoids did not contain abnormal cells.

Corresponding to the gross lesions of the lung were necrotic areas of various ages crowded with cryptococci and devoid of inflammatory reaction. In some areas alveoli were distended with organisms, adjacent to relatively small foci of necrosis; in others, necrosis was more extensive than parasitic infiltration. No constant relation to the bronchi or vasculature could be determined. Only occasional small areas of peribronchial inflammation were present. No pneumonic process was found. The pleural foci noted grossly consisted similarly of necrosis and masses of cryptococci. These foci were incompletely ringed with plasma cells; small underlying areas were atelectatic.

The lesions of the colon were similar to those of the pleura. They occupied the remnants of the mucosa and most of the submucosa and were continuous with fibrinous deposits replacing the surface epithelium. Some of the necrotic

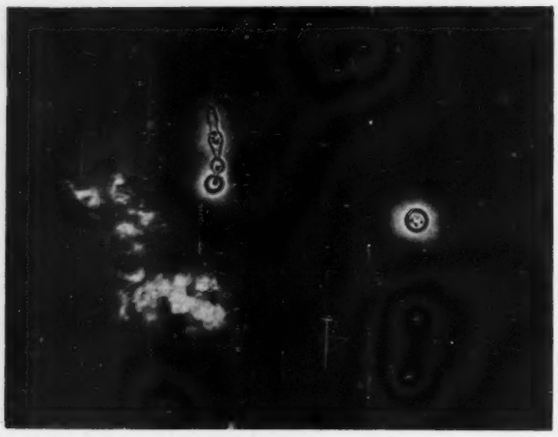


FIG. 7. Cryptococci in India ink smear from cut surface of formalin-fixed lung; × 780.

foci appeared to have originated in lymph follicles. Heaps of plasma cells were found in the submucosa. Submucosal veins were necrotic in places. Cryptococci were abundant in the necrotic areas.

The kidneys showed numerous irregularly distributed foci of cryptococcal invasion and necrosis as did the lungs and colon. In addition there was widespread atrophy of tubules, with moderate fibrosis and round cell infiltration.

Leukemic infiltrations could not be identified in the bone marrow but numerous small fibrinous and necrotic foci were noted, no cryptococci being seen with certainty. Sections from the blood vessels of the calf showed thick-walled artery and vein with old thromboses and surrounding non-specific inflammatory reaction.

Sections from cerebral cortex, cerebellum, basal ganglia, pons, medulla, cord and meninges revealed no parasites or necrosis. Small numbers of mononuclear cells were found diffusely in the leptomeninges.

Cultures for cryptococci were not carried out since the diagnosis was not suspected at the time of autopsy. Tissue slides were submitted to Dr. Norman F. Conant,[1] who advanced the diagnosis of crytococcosis, and suggested India ink smears of scraped tissue for confirmation. India ink smears from formalin-fixed lung scrapings (Fig. 7) revealed the fungus as a thick-walled, spherical, budding, yeast-like cell, 8 to 13 micra in diameter, surrounded by a wide capsule.

Pathologic diagnoses were as follows: (1) Generalized torulosis (cryptococcosis) with greatest involvement in lungs, intestine, lymph nodes and kidneys; (2) enlargement of the spleen; (3) ascites and hydrothorax, bilateral; (4) cholelithiasis; (5) old thromboses in artery and vein of leg and (6) chronic leptomeningitis.

COMMENTS

The patient presented clinically what appeared to be an obvious example of granulocytic leukemia. Even in retrospect there seems little to indicate the need for a search for any other disease. Yet three unusual phenomena were noted and commented upon during life. One of these was the difficulty in placing the case into the category of either acute or chronic leukemia. The large spleen, the high leukocyte count reaching 341,000 per cu. mm., the increase in basophils to 5 per cent on May 2nd, the normal thrombocyte count of April 1st and the moderate degree of anemia were characteristic of chronic granulocytic leukemia. The rapid course, high fever and cachexia were characteristic of acute leukemia as were the finding of over 80 per cent myeloblasts in the peripheral blood, the later thrombocytopenia, the early appearance of anemia and its transient severity, the rarity of eosinophils in the peripheral blood and the paucity of intermediate maturation forms of granulocytes in the marrow (hiatus leukaemicus). Leukocyte counts above 100,000 per cu. mm. are unusual in acute leukemia whereas with the higher counts of chronic granulocytic leukemia there are usually moderate increases in basophils, eosinophils and, early in the course, in thrombocytes as well. Against an acute phase of chronic granulocytic leukemia were the absence of intermediate maturation forms and the high percentage of blast forms but favoring it was the large spleen (except for its terminal reduction in size). Blast forms are usually less than 20 per cent in acute exacerbations of chronic granulocytic leukemia.

While bleeding phenomena are common in leukemia, thromboses of large vessels are rarely mentioned in descriptions of the disease and have not been encountered in our experience. The patient's bilateral thrombophlebitis with its repeated exacerbations was therefore puzzling.

The third unusual phenomenon noted was the remarkable shrinking and final disappearance to palpation of the spleen during the last month of life. This was not due to any marked development of ascites and remained unexplained since it is not expected in the terminal stage of leukemia. It was accompanied with hematologic remission of the leukemia despite the continuing cachectic course.

These unusual findings did not seem sufficiently important in themselves to make us question the validity of the diagnosis of leukemia which appeared so well established. They might, however, have led us to look for complicating factors. Procedures which might have been undertaken in a search for cryptococci, had their presence been suspected, include biopsies and cultures of liver, spleen and lymph nodes, and cultures of bone marrow, pleural fluid and sputum. From the autopsy evidence the chance for success with these procedures would have been small, except in the case of pleural fluid and lymph nodes. The chylous appearance of the later pleural fluids was attributed to lymphatic obstruction by leukemic infiltrations but may well have represented quantities of gelatinous cryptococci which we failed to observe. Examination and culture of spinal fluid, the most frequent means of diagnosing cryptococcosis during life, would not have been helpful inasmuch as our case lacked meningeal invasion at postmortem examination.

The absence of leukemic infiltration of the bone marrow at autopsy leads one naturally to the conclusion that the hematologic findings during life represented a leukemoid reaction to the cryptococcic infection. Yet the clinical syndrome was far more typical of true granulocytic leukemia than of a leukemoid reaction as usually observed. The elevated basal metabolism, the high blood uric acid and the three positive marrow smears, one of which was taken from the spinous process of a vertebra, are not usual in leukemoid reactions. The marked immaturity of the granulocytes was in contrast to the usual predominance of mature forms seen in leukemoid reactions. The high percentage of blast forms in the circulating blood, the anemia and the thrombopenia are all characteristic of acute leukemias and rare in leukemoid reactions. The leukocyte count reached a height (341,000) remarkable for a leukemoid reaction. Even had cryptococcosis been diagnosed during life we would have retained the diagnosis of granulocytic leukemia as well.

Block and Jacobson[2] have pointed out the ease with which myeloid metaplasia may be confused with granulocytic leukemia in the presence of a hyperplastic marrow. However, our case had few or no normoblasts in the peripheral blood, a pronounced myeloblastic picture and a leukemic hiatus, in contrast to the findings in myeloid metaplasia, and at autopsy no myeloid metaplasia was found.

A case of torulosis in which a clinical diagnosis of chronic granulocytic leukemia was made has been reported by Cawley, Grekin and Curtis[3] (Case 1). Their brief autopsy report makes no mention of leukemic infiltrations but visceral and nervous system torulosis was present. These authors also mention two additional cases of granulocytic leukemia and one of monocytic leukemia, with microscopic evidence of torulosis discovered at necropsy, encountered at the University of Michigan Hospital within recent years. Whether leukemic infiltrations existed at necropsy in these cases is not mentioned.

Case v of the previously mentioned authors presented both clinical and autopsy evidence of chronic lymphatic leukemia as well as torulosis. These five cases of leukemia occurred among nine cases of cryptococcosis.[4] Such an association is indeed startling and suggests a specific relationship between the two. Magruder[5] reported a case of torulosis associated with chronic lymphatic leukemia. Hodgkin's disease and lymphoblastoma have been reported not infrequently as coexistent with torulosis. Gendel, Ende and Norman[6] found fourteen instances of such association in reviewing 165 reported cases of cryptococcosis.

Sufficient evidence is available to indicate that leukemic processes can be influenced by chemical agents. Remissions other than by destruction of hematopoietic tissue have been produced by urethane, folic acid antagonists, leukemic urine extracts and adrenotrophic hormone. Leukemic syndromes have been produced experimentally by the injection of extracts of urine from patients with leukemia, by various chemical agents, carcinogens, roentgen rays and estrogens. Our use of a crude lymphokentric acid preparation extracted from the urine of a patient with chronic lymphocytic leukemia was an attempt to influence the course of the disease by inhibiting production of granulocytes.[7] However, Figure 1 indicates that the terminal remission was already under way when this was instituted and the amount of the preparation used was probably too small to elicit more than minimal effect. In observations on exsanguinotransfusion in three cases of granulocytic leukemia Piney[8] found prompt reduction in the number of immature cells suggesting that some constituent of normal blood exerts an effect on abnormal leukopoiesis. Viruses have been found

to exert an antagonist action toward experimental lymphoid tumors with resulting immunity.[9]

In view of the susceptibility of the leukemic process to such chemical influences and the unusual association of leukemias and lymphoblastomas with mycoses, is it not possible that chemical constituents, secretions or reaction products of some of the pathogenic yeasts and molds may influence the development or disappearance of the leukemic state? That leukemias may be curable is indicated by Forkner's review,[10] in 1938 of reported recoveries. After discarding most such reports as insufficiently studied, four cases of apparent recovery remained, three of acute leukemia and one of chloroma. One should not overlook the possibility, however remote, that the cryptococcic infection may have first stimulated, then terminated, a leukemic response in our case. The hematologic course indicates a remission beginning approximately one month before death. A remarkable shrinking of the spleen occurred concomitantly and suggests reticulo-endothelial remission. Such early stimulation followed with depression is not an unusual pharmacologic mode of action of many drugs on various physiologic functions.

Involvement of the central nervous system is the most constant feature of systemic cryptococcosis in previously reported cases. Voyles and Beck,[11] reviewing the literature in 1946, state that it is invariably the cause of death. Cases limited to the lungs are not infrequent and the lung is believed to be the portal of entry of the infection. Wade and Stevenson[12] were unable to produce involvement of the central nervous system in mice without visceral involvement, chiefly of the lung and kidney and less frequently of the liver and spleen, indicating that cryptococcosis is a true septicemia. Human cases limited to the nervous system are frequent, however, indicating probably the relative susceptibility of this system to the infection. Our case may be unique in showing visceral dissemination without central nervous system involvement. Case II of Voyles and Beck[11] showed only slight involvement of the nervous system, with dominant visceral findings at autopsy but neurologic involvement was evident clinically and cryptococci were found in the meninges. Mild chronic leptomeningitis, as found in our patient at autopsy, occurs in a variety of conditions of which generalized infections represent one group.

SUMMARY

A case of visceral cryptococcosis without central nervous system involvement presented during life the picture of granulocytic leukemia. Hematologic and reticulo-endothelial remission occurred during the last month of life and leukemic infiltrations were absent at postmortem examination.

REFERENCES

1. Conant, N. F. Personal communication.
2. Block, M. and Jacobson, L. O. Myeloid metaplasia. *J. A. M. A.*, 143: 1390–1396, 1950.
3. Cawley, E. P., Grekin, R. H. and Curtis, A. C. Torulosis. A review of the cutaneous and adjoining mucous membrane manifestations. *J. Invest. Dermat.*, 14: 327–344, 1950.
4. Zarafonetis, C. J. Discussion of Smith, D. T. Fungous infections in the United States. *J. A. M. A.*, 141: 1223–1226, 1949.
5. Magruder, R. G. Report of three cases of torula infection of central nervous system. *J. Lab. & Clin. Med.*, 24: 495–499, 1939.
6. Gendel, B. R., Ende, M. and Norman, S. L. Cryptococcosis, a review with special reference to apparent association with Hodgkin's disease. *Am. J. Med.*, 9: 343–355, 1950.
7. Miller, F. R. and Turner, D. L. The action of specific stimulators on the hematopoietic system. *Am. J. M. Sc.*, 206: 146–158, 1943.
8. Piney, A. Remissions in acute leukemia: the role of blood transfusion in treatment. *Acta hemat.*, 3: 1–16, 1950.
9. Sharpless, G. R., Davies, M. C. and Cox, H. R. Antagonistic action of certain neurotropic viruses toward a lymphoid tumor in chickens with resulting immunity. *Proc. Soc. Exper. Biol. & Med.*, 73: 270–275, 1950.
10. Forkner, C. E. Leukemia and Allied Disorders. New York, 1938. The Macmillan Company.
11. Voyles, G. Q. and Beck, E. M. Systemic infection due to torula histolytica (Cryptococcus hominis). I. Report of four cases and review of the literature. *Arch. Int. Med.*, 77: 504–515, 1946.
12. Wade, L. J. and Stevenson, L. D. Torula infection. *Yale J. Biol. & Med.*, 13: 467–476, 1941.

straining at stool:

always distressing . . .
frequently dangerous
. . . sometimes deadly

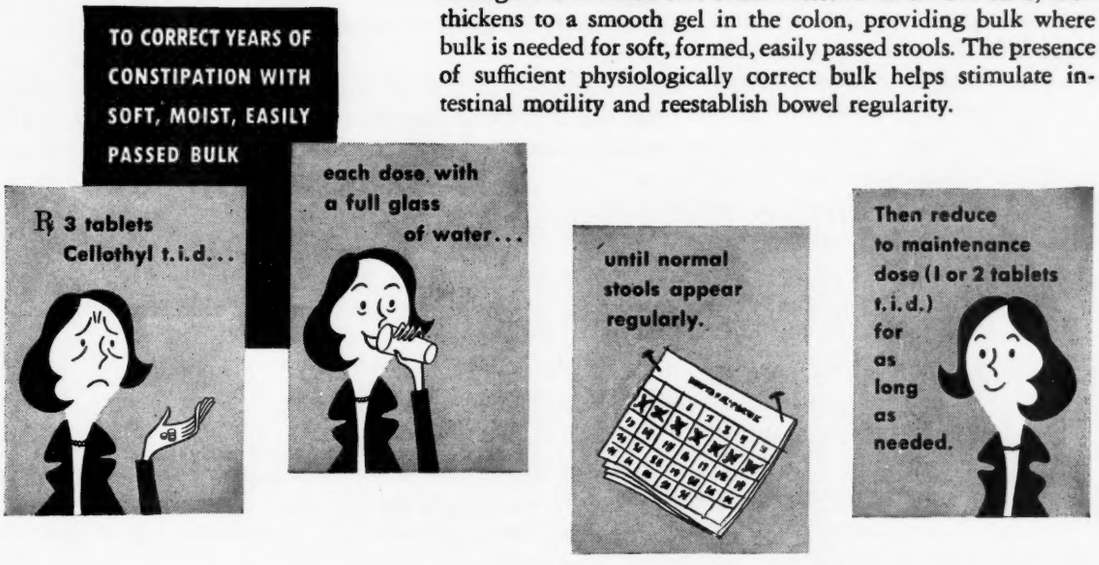
The very states in which straining at stool can be most dangerous are conditions which invite constipation: cardiac dysfunction, hernia, pregnancy, anorectal disease and postsurgical states. In their presence, such almost unavoidable factors as inactivity, dietary restriction, weakness and local trauma lead to constipation due to bowel stasis, bulk deficiency or dyschezia.

Prevention of the need to strain has become an important part of therapy in such states. Fortunately, natural, comfortable bowel function can be achieved and maintained with Cellothyl without fear of interference with other therapeutic measures or of inducing cathartic addiction.

Where constipation exists, it can be corrected with Cellothyl; where it is likely to occur, it can be prevented. The ease and frequency of bowel movements improves as Cellothyl reestablishes normal function by correcting several common and related factors:

1. ***bulk deficiency*** *. . . by providing adequate bulk of proper consistency*
2. ***intestinal stasis*** *. . . by encouraging peristaltic action through gentle mechanical stimulation*
3. ***dyschezia*** *. . . by assuring soft, moist, easily passed stools.*

The physician using Cellothyl has the advantage of providing medication which is nontoxic, nonantigenic and nonreactive in the gastrointestinal tract. It causes no bloating or distention, no frequent, urgent calls to stool. Its action is physiologically correct. Following the normal digestive gradient, Cellothyl passes through the stomach and small intestine in a fluid state, then thickens to a smooth gel in the colon, providing bulk where bulk is needed for soft, formed, easily passed stools. The presence of sufficient physiologically correct bulk helps stimulate intestinal motility and reestablish bowel regularity.



Cellothyl® BRAND OF METHYLCELLULOSE ESPECIALLY PREPARED BY THE CHILCOTT PROCESS

***Cellothyl* tablets (0.5 Gram) in bottles of 100, 500 and 5000.**

CHILCOTT *Laboratories* DIVISION OF The Maltine Company

MORRIS PLAINS, NEW JERSEY

for Control

in Sedation and Hypnosis...

Neuronidia®

(Elixir of diethylmalonylurea — Schieffelin)

Neuronidia is an effective sedative and hypnotic. It may be safely used in insomnia, hysteria, neurasthenia, thyroid diseases, chorea and mental disturbances. *Neuronidia* is indicated in virtually all cases of nervous disturbances uncomplicated by pain.

Pharmacological and clinical research have demonstrated that the depth and degree of sedation and hypnosis can be readily controlled with barbital, the active ingredient of

NEURONIDIA

Neuronidia contains per teaspoonful:
0.13 Gm. diethylmalonylurea

Dosage: Orally, as a sedative
½ to 1 teaspoonful repeated as indicated
As a hypnotic
2 teaspoonfuls before retiring

℞ Sodium salicylate ʒIV
Neuronidia ʒIV

Sig: *To induce sleep and produce analgesia*
one dessertspoonful at bedtime.
For sedation and analgesia
One teaspoonful two or three times daily as required.

Supplied: Bottles of 8 fluid ounces, and 1 gallon

Professional samples and literature are available on request.

Schieffelin & Co. since 1794 / *pharmaceutical and research laboratories*
24 Cooper Square, New York 3, N. Y.

VERILOID* INTRAVENOUS

Immediate prolonged control of arterial tension through the intravenous route

The administration of Veriloid Intravenous to the patient in a hypertensive crisis produces—in a matter of minutes—a dramatic drop of arterial tension to normal or near-normal limits. For the first time, the physician now has available a potent hypotensive alkaloidal fraction of Veratrum capable of producing any desired degree of blood pressure reduction, with definite control of the intensity and duration of its action.

A Must for the Emergency Bag

Since Veriloid Intravenous makes possible immediate controlled reduction of both systolic and diastolic tension to any desired levels, it is indicated in the emergency treatment of hypertensive states accompanying cerebral vascular accidents, malignant hypertension, hypertensive crises (encephalopathy), and hypertensive states after coronary occlusion.

Veriloid Intravenous, a biologically standardized hypotensive fraction of Veratrum viride, is supplied in 5 cc. and 20 cc. ampuls, each cc. containing the equivalent of 0.4 mg. of Veriloid standard reference powder. Complete information regarding dosage and rate of administration is contained in the circular which accompanies each ampul of Veriloid Intravenous. Detailed literature promptly supplied on request.

*Trade-Mark of Riker Laboratories, Inc.

RIKER LABORATORIES, INC., 8480 Beverly Blvd., Los Angeles 48, California

HIGH LOCAL
Decongestive Action

Wyeth®

LOW SYSTEMIC
Stimulant Effect

Extensive tests show that Wyamine decongests and maintains shrinkage of nasal mucosa—up to three hours. Clinical evidence confirms, too, that Wyamine is remarkably low in cerebral stimulant effects . . . brings quick relief and allows restful sleep.

Available as: Solution Wyamine Sulfate, Bottles of 1 fl. oz.

Wyamine-Tyrothricin Nasal Solution, Bottles of 1 fl. oz.—with dropper or JETOMIZER®.

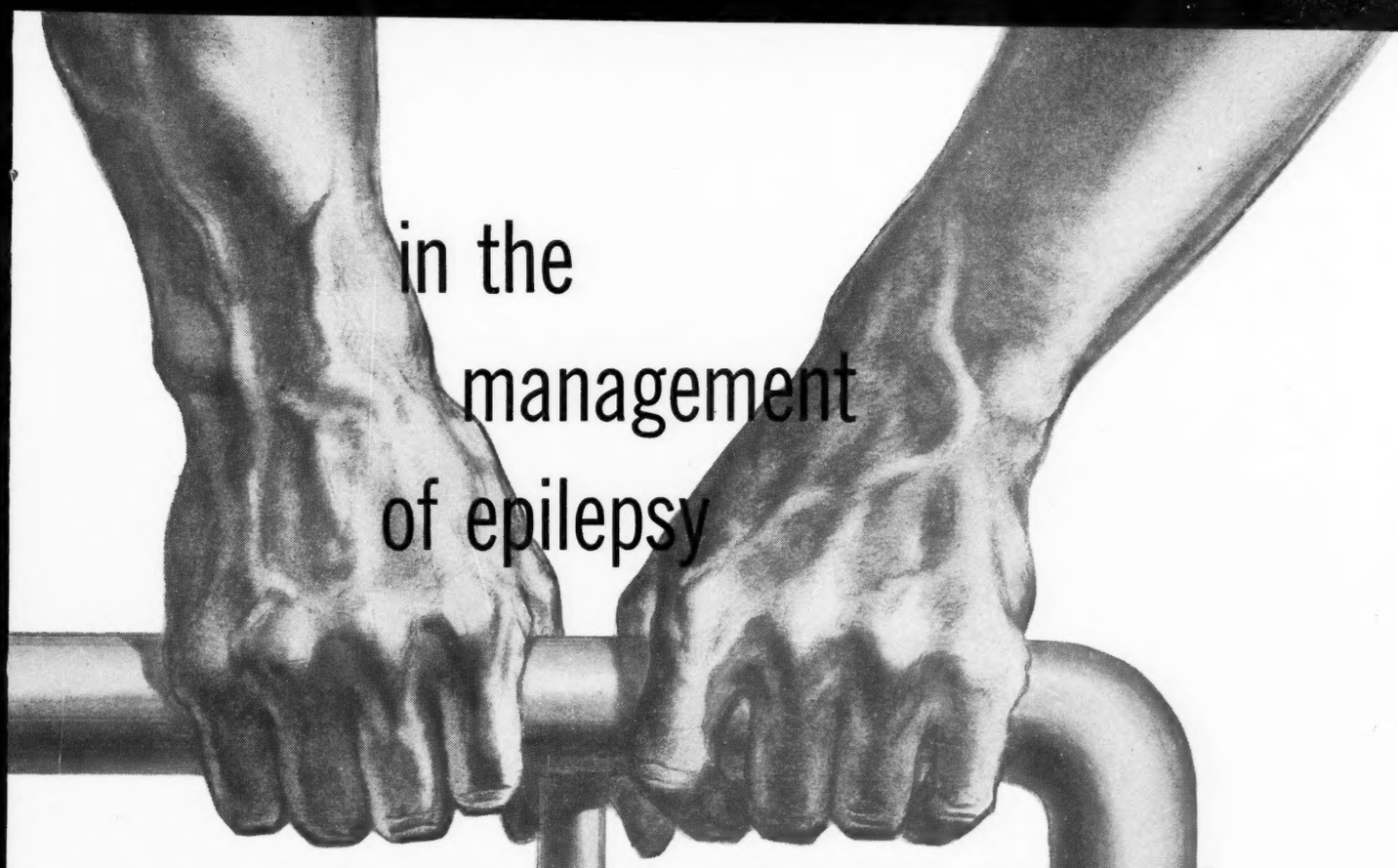
Wyamine-Penicillin, Capsules, Penicillin with Vasoconstrictor, for preparation of nasal solutions.

WYAMINE®

Mephentermine

N-methylphenyl—*tertiary*—butylamine WYETH

Wyeth Incorporated, Philadelphia 2, Pa.



in the management of epilepsy

DILANTIN®

"... little depression

... strong opposition to major convulsions."

"The introduction of diphenylhydantoin
was a marked advance in therapy, because this drug,
although distantly related to the barbiturates,
produced little depression while exerting strong
opposition to major convulsions."*

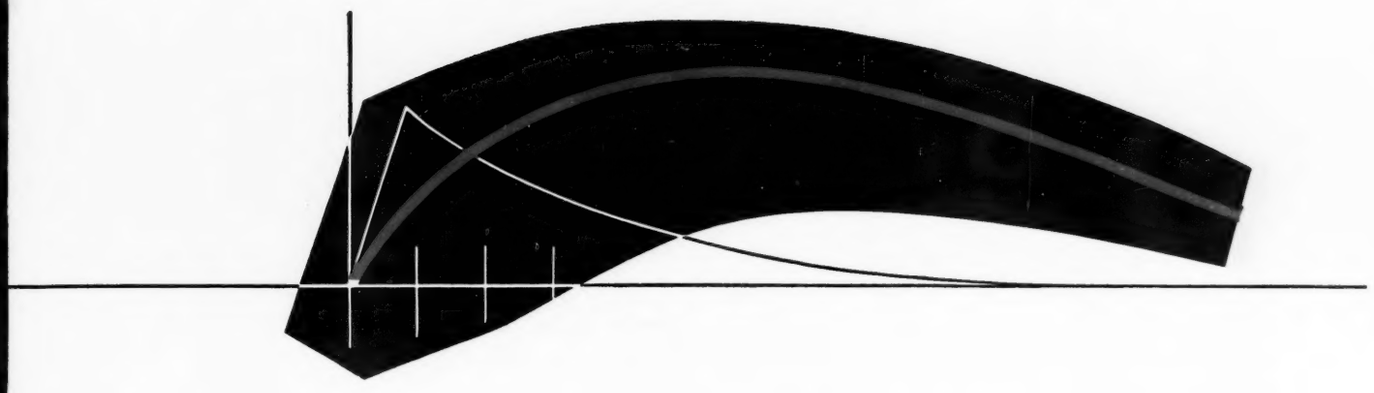
Extensive clinical experience confirms the finding that DILANTIN – producing little or no depression – prevents seizures or greatly reduces their number and severity in the majority of epileptic patients.

DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis)
is available in Kapseals® of 0.03 Gm. (½ gr.) and
0.1 Gm. (1½ gr.) in bottles of 100 and 1000.

*Cutting, W. C.: A Manual of Clinical Therapeutics, ed. 2, Philadelphia, W. B. Saunders & Co., 1948, p. 484.

PARKE, DAVIS & COMPANY

MEDICAMENTA VERA



ACTHAR* *Gel*

LONG-ACTING

ACTHAR *Gel*, the new LONG-ACTING repository preparation for deep subcutaneous and intramuscular injection, greatly facilitates ACTH therapy for both the patient and the physician. A single daily injection is sufficient in the many cases requiring less than 80 I.U. (mg.) per day. Remission of symptoms may often be maintained by two to three injections per week. Office treatment for the ambulatory patient and home treatment for the bedridden become readily applicable, with considerable economy to the patient. ACTHAR *Gel* is well-tolerated locally and possesses the full efficacy of aqueous ACTHAR.

Indications: Rheumatoid arthritis, rheumatic fever, acute lupus erythematosus, drug sensitivities, severe bronchial asthma, contact dermatitis, most acute inflammatory diseases of the eye, acute pemphigus, exfoliative dermatitis, ulcerative colitis, acute gouty arthritis, secondary adrenal cortical hypofunction.

Literature and directions for administration of ACTHAR *Gel*, including contraindications, available on request.

*THE ARMOUR LABORATORIES BRAND OF ADRENOCORTICOTROPIC HORMONE (A.C.T.H.)

THE ARMOUR LABORATORIES • CHICAGO 11, ILLINOIS

world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

AT THE FIRST SNEEZE

That's the sign for SYNTHENATE TARTRATE therapy ... for, in the early phase of coryza, this simple treatment brings gratifying, often dramatic relief.

In 65% of cases complete remission of symptoms occurs within fifteen minutes after injection of 1 cc of SYNTHENATE TARTRATE-Breon, when administered within twenty-four hours of the first sign of a cold!

Injection is simple...relatively nontoxic...prolonged in effect. SYNTHENATE TARTRATE-Breon increases cardiac efficiency and frequently slows the pulse rate; thus it is effective without appreciably increasing the work of the heart. It does not cause cardiac arrhythmias, does not stimulate the central nervous system, does not produce signs of anxiety.

DOSAGE: 1 cc injected intramuscularly or subcutaneously ... repeated in 3 or 4 hours, if required.

SYNTHENATE

Trademark

TARTRATE SOLUTION

Available at all drug stores. 1 cc ampuls —boxes of 12 and 25.
Complete literature to physicians on request.

BREON

George A. Breon & Co.

Pharmaceutical Chemists • 1450 Broadway, New York 18, N.Y.

CYCOTIN

CURBS HUNGER AND APPETITE

Quickly, Safely, Effectively

With an estimated† 25,000,000 American adults overweight, the medical profession shoulders a heavy responsibility in advising those who seek their help as to how to eliminate the excess poundage. Since "the one consistent and demonstrable finding in obesity is overeating,"* an important key to successful management is obviously control of appetite.

Cycotin exerts dual anoretic action. Note the:

HIGH methylcellulose content

(500 mg. per tablet)—quickly imparts a sense of fullness by providing non-nutritive intestinal bulk; also increases moisture of stool.

LOW d-amphetamine phosphate content

(1.67 mg. per tablet)—moderate dosage usually obviates or materially reduces undesirable side-effects.

DOSAGE: Initially, 3 tablets t.i.d. with a full glass of water ½ hour before meals—adjust to individual requirements for proper maintenance.

REED & CARNRICK

FOUNDED IN 1860 — R AND C — JERSEY CITY 6, N. J. TORONTO, ONT.

†Metropolitan Life Insurance Co.
*M. Clin. North Am. 35:483, 1951.

Verified by Clinical Evidence—
Safer, More Dependable Cardiac Therapy

Myocardone

Announced at the 41st annual meeting of the American Society for Pharmacology and Experimental Therapeutics, MYOCARDONE marks another important advancement in the search for the hormonal control of cardiac function.

Carefully controlled clinical investigations suggest that MYOCARDONE—a new derivative of heart muscle—notably improves the functional efficiency of the heart through cardiotonic and vasodilator actions.

The most recent study involved a group of 58 patients with various cardiac disturbances including:

Cardiac Decompensation — 24 patients with dyspnea, dependent edema, pulmonary congestion, orthopnea and hepatomegaly.

Results with MYOCARDONE: More than half showed definite improvement.

Hypertension Without Decompensation —10 patients with symptoms due to hypertension (dizziness, headache, throbbing, visual disturbance).

Results with MYOCARDONE: ". . . 6 of the 10 enjoyed relief of the distressing symptoms when taking MYOCARDONE . . ."

Compensated Arteriosclerotic Heart Disease —5 patients who had compensated on routine management.

Results with MYOCARDONE: "Three (60%) of the compensated arteriosclerotics maintained compensation with MYOCARDONE alone."

Angina Pectoris—19 patients with precordial pain aggravated by exertion and emotional tension.

Results with MYOCARDONE: "Definite improvement resulted in two-thirds of the anginal cases."

This report further emphasized:

Efficacy ". . . When MYOCARDONE was administered there was definite subjective and clinical improvement."

Safety "There were virtually no side effects." "All patients tolerated MYOCARDONE well."

Prolonged Results "Patients whose response to MYOCARDONE was satisfactory continued to do well for from 2 weeks to several months after the drug was withheld."

Digitalis-Nitrite Replacement

MYOCARDONE advantageously replaces or supplements digitalis therapy. Reduces or eliminates the need for nitrites in angina pectoris.

Literature on request

Chemico LABORATORIES, INC.
Indianapolis 20, Indiana

Terramycin

ointment

Crystalline Terramycin Hydrochloride Ointment is recommended for topical therapy of superficial pyogenic infections, pustular dermatitis, minor wounds and burns. In severe or deep-seated infections, topical treatment is suggested as an adjunct to oral Terramycin therapy. Well tolerated, and stable at room temperature, Terramycin Ointment is effective and safe for continued use.

Supplied: | *30 mg. per Gm. ointment; tubes of 1 oz. and 1/2 oz.*

ANTIBIOTIC DIVISION *Pfizer* CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

regulate cardiac output...more precisely

Digitaline Nativelle provides *positive maintenance*—positive because it is completely absorbed and uniformly dissipated. It affords full digitalis effect between doses. Since the non-absorbable glycosides, so frequently causing gastric distress, are eliminated, untoward side reactions are rare. Because of this efficiency Digitaline Nativelle is a cardiotonic of choice of leading cardiologists the world over. For the comfort and protection of your patients—for your own assurance—specify Digitaline Nativelle in full when you prescribe.

digitaline nativelle

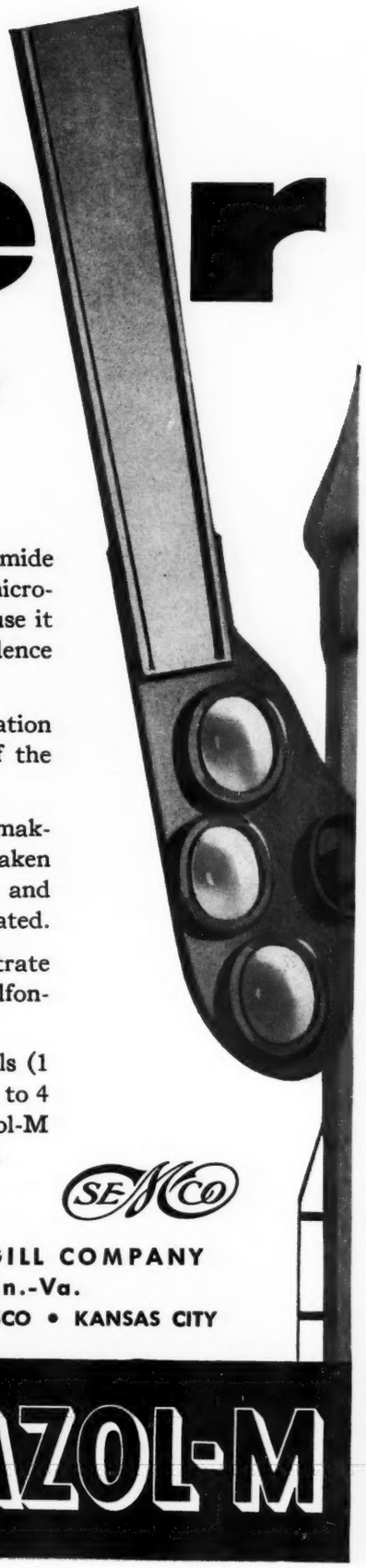
Chief active principle of digitalis purpurea (digitoxin)
(not an adventitious mixture of glycosides)

For dosage instructions consult Physicians' Desk Reference

Send for brochure:
"Modern Digitalis Therapy"
Varick Pharmacal Company, Inc.
(Division of E. Fougera & Co. Inc.)
75 Varick St., New York

safer

in Sulfonamide Therapy



Aldiazol-M brings a high degree of safety to sulfonamide therapy. This alkalizing suspension of equal parts of microcrystalline sulfadiazine and sulfamerazine is safer because it decreases the danger of crystalluria and reduces the incidence of allergic reactions. It offers these advantages:

Greater Efficacy, achieved through decreased acetylation of the absorbed sulfonamides, and rapid absorption of the microcrystalline form.

Highly Palatable. Aldiazol-M is pleasantly flavored, making it acceptable to virtually all patients. It is readily taken by children, making for universal patient cooperation and permitting its use whenever sulfonamide therapy is indicated.

Greater Urinary Solubility is produced by sodium citrate which increases urinary solubility of the combined sulfonamides by more than 400%.

The maintenance dose of Aldiazol-M is 2 teaspoonfuls (1 Gm. of total sulfonamides) every 4 hours; initial dose, 2 to 4 teaspoonfuls (3 to 6 Gm. of total sulfonamides). Aldiazol-M is available at all pharmacies in pint and gallon bottles.

SE M CO

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

Formula

Each teaspoonful (5 cc.) of Aldiazol-M contains:

Sulfadiazine (microcrystalline)	0.25 Gm.
Sulfamerazine (microcrystalline)	0.25 Gm.
Sodium Citrate	1.0 Gm.

ALDIAZOL-M

one-word prescription | for the dry and unproductive cough

A POTENT analgesic and antitussive, due to its content of dihydrocodeinone —a codeine derivative of greatly enhanced activity, remarkably free from nausea and constipation—

plus the

ANTIHISTAMINIC action provided by Pyra-Maleate (VB brand of Pyranisamine Maleate)—an effective antihistaminic with a high index of safety—

plus the

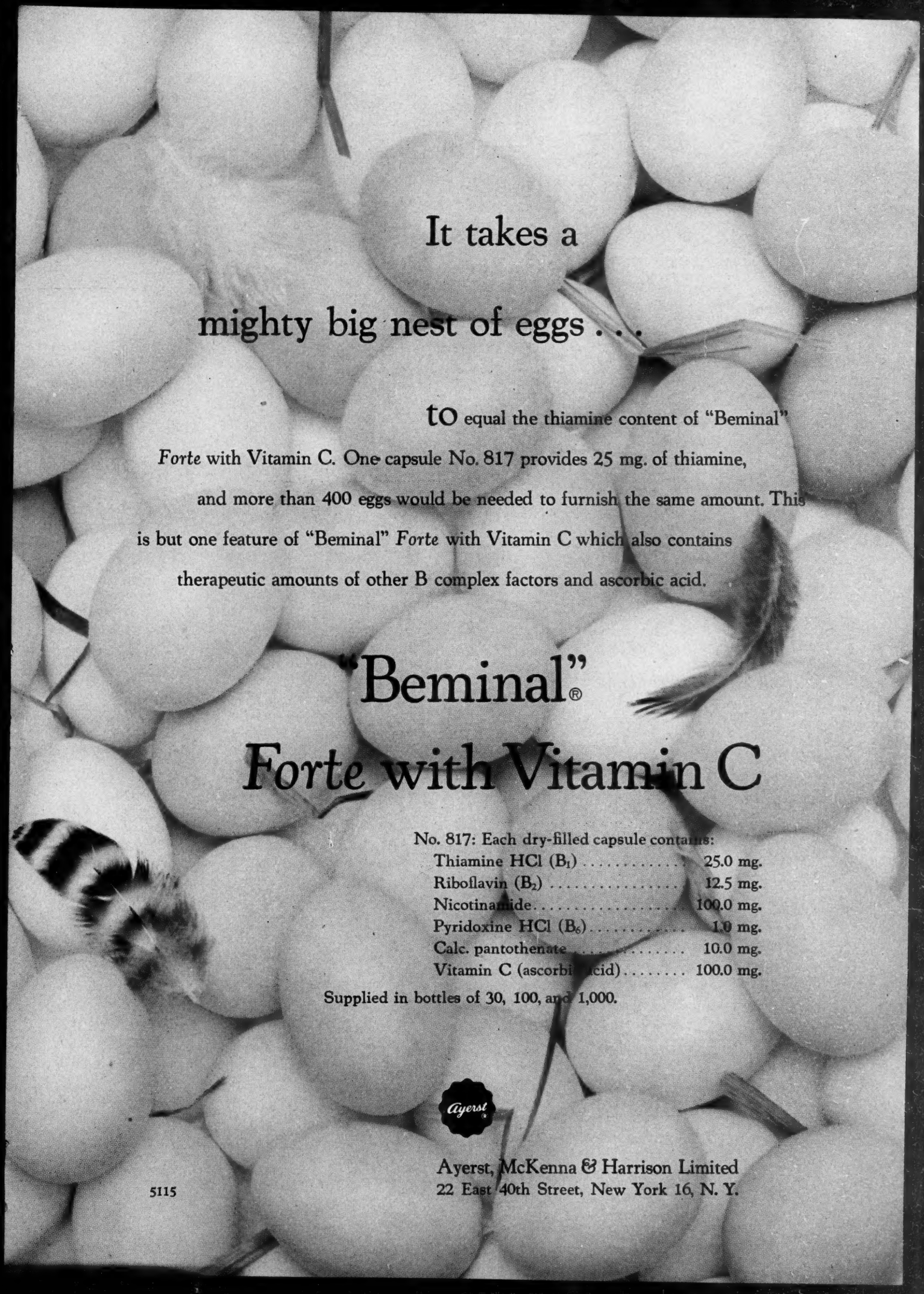
EXPECTORANT properties of ammonium chloride and citric acid . . . in a soothing, mentholated syrup vehicle.

Supplied in 1 pint bottles. An exempt narcotic preparation.

VB

Write for detailed information

VANPELT & BROWN, Inc. *Pharmaceutical Chemists* **RICHMOND 4, VA.**


It takes a
mighty big nest of eggs . . .
to equal the thiamine content of "Beminal" *Forte* with Vitamin C. One capsule No. 817 provides 25 mg. of thiamine, and more than 400 eggs would be needed to furnish the same amount. This is but one feature of "Beminal" *Forte* with Vitamin C which also contains therapeutic amounts of other B complex factors and ascorbic acid.
"Beminal"®
Forte with Vitamin C
No. 817: Each dry-filled capsule contains:
Thiamine HCl (B_1) ..... 25.0 mg.
Riboflavin (B_2) ..... 12.5 mg.
Nicotinamide ..... 100.0 mg.
Pyridoxine HCl (B_6) ..... 1.0 mg.
Calc. pantothenate ..... 10.0 mg.
Vitamin C (ascorbic acid) ..... 100.0 mg.
Supplied in bottles of 30, 100, and 1,000.
Ayerst
Ayerst, McKenna & Harrison Limited
22 East 40th Street, New York 16, N. Y.
5115

Duo...

for complementary effects wherever combined estrogen-androgen therapy is indicated...

e. g. *In fractures and osteoporosis in either sex to promote bone development, tissue growth, and repair.*

e. g. *In the female climacteric in certain selected cases.*

e. g. *In dysmenorrhea in an attempt to suppress ovulation on the basis that anovulatory bleeding is usually painless.*

e. g. *In the male climacteric to reduce follicle-stimulating hormone levels.*

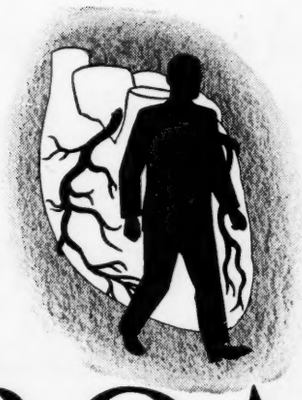
"PREMARIN"® *with* METHYLTESTOSTERONE

is designed to permit utilization of both the complementary and the neutralizing effects of estrogen and androgen when administered concomitantly. Thus certain properties of either sex hormone may be employed in the opposite sex with a minimum of side effects.
Availability: Each tablet provides estrogens in their naturally occurring, water-soluble, conjugated form expressed as sodium estrone sulfate, together with methyltestosterone.

No. **879**—Conjugated estrogens equine ("Premarin") ..... 1.25 mg.
Methyltestosterone ..... 10.0 mg.
Bottles of 100 tablets (yellow)

No. **878**—Conjugated estrogens equine ("Premarin") ..... 0.625 mg.
Methyltestosterone ..... 5.0 mg.
Bottles of 100 tablets (red)

Ayerst, McKenna & Harrison Limited • 22 East 40th Street, New York 16, New York



a most significant advance

TROMEXAN T. M.

ethyl acetate

new, safer, oral anticoagulant

Throughout the exhaustive studies on TROMEXAN, involving many hundreds of cases, this new anticoagulant has proved singularly free from the dangers of hemorrhagic complication. Other advantageous clinical features of TROMEXAN are:

1 ***more rapid therapeutic response***
(therapeutic prothrombin level in 18-24 hours);

2 ***smooth, even maintenance of prothrombin level***
within therapeutic limits;

3 ***more rapid return to normal***
(24-48 hours) after cessation of administration.

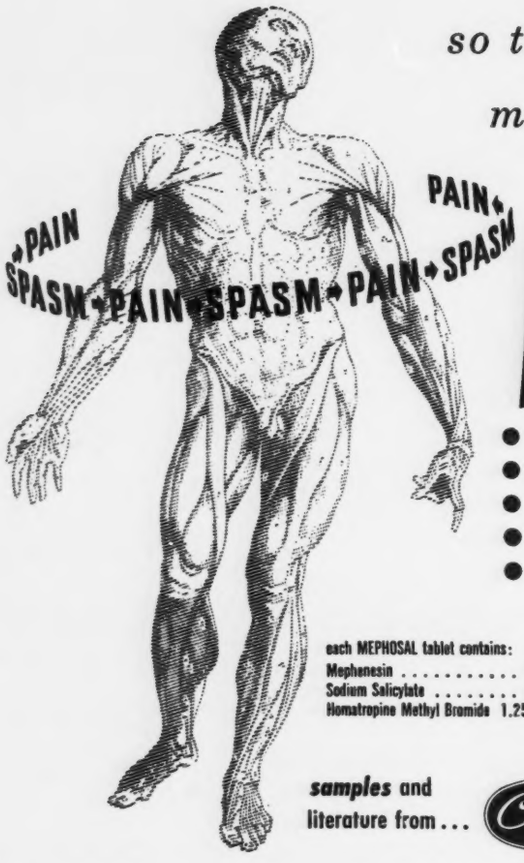
In medical and surgical practice . . . as a prophylactic as well as a therapeutic agent . . . TROMEXAN extends the scope of anticoagulant treatment by reducing its hazards.

Detailed Brochure Sent on Request.

TROMEXAN (brand of ethyl biscoumacetate): available as uncoated scored tablets, 300 mg., bottles of 50 and 250.

Geigy

GEIGY PHARMACEUTICALS • Division of Geigy Company, Inc.
220 Church St., New York 13, N.Y.



so the ***rheumatic*** *patient*
may ***move, walk*** *and* ***live*** *in*
greater comfort

MEPHOSAL

- **relieves pain promptly**
- **helps abolish muscle spasm**
- **minimizes postural deformities**
- **increases ease and range of motion**
- **allays concomitant gastro-intestinal distress**

each MEPHOSAL tablet contains:

Mephenesin	125 mg. (2 gr.)
Sodium Salicylate	125 mg. (2 gr.)
Homatropine Methyl Bromide	1.25 mg. (1/50 gr.)

prescribe *safe, non-toxic* MEPHOSAL *in stiff neck, night cramps, sacroiliac pains, low back pain, sciatica, rheumatoid and osteo-arthritis, etc.*

samples **and literature from...** Crookes

CROOKES LABORATORIES, INC.
305 EAST 45 ST., NEW YORK, N.Y.

---

new dosage form

for the bag

*Dilaudid** sulfate

10 cc. Multiple Dose Vial

Each cc. contains 2 mg. (1/32 gr.) dihydromorphinone (Dilaudid) sulfate in sterile solution—convenient and ready for instant use.

Dilaudid—a powerful analgesic—dose, 1/32 grain to 1/20 grain.
a potent cough sedative—dose, 1/128 grain to 1/64 grain.
an opiate, may be habit forming.

•Dilaudid is subject to Federal narcotic regulations.
*Dilaudid®, E. Bilhuber, Inc.

BILHUBER-KNOLL CORP. ORANGE, NEW JERSEY, U. S. A.

new

Schering ANNOUNCES

DORMISON*

new, non-barbiturate hypnotic

for safe, sound sleep
without drug hangover
free from habit-forming properties
of the barbiturates

safe
free from habit-forming or addiction properties of barbiturates; rapidly metabolized; no cumulative action; no toxic effects on prolonged use

acts gently and quickly in insomnia
mild hypnotic action quickly induces restful sleep

no prolonged suppressive effect
action subsides after a few hours; patient continues to sleep naturally

no drug hangover
patient awakens refreshed with no "drugged" feeling

DORMISON is a substance new to pharmacology, completely different from barbiturates and other hypnotics. It contains only carbon, hydrogen and oxygen. It has no nitrogen, bromine, urea residues, sulfone groups or chemical configurations present in depressant drugs now in use.

The usual dose of DORMISON (methylparafynol†) is one or two capsules, taken just before the patient is ready for sleep. DORMISON's wide margin of safety allows liberal adjustment of dosage until the desired effect is obtained. DORMISON is supplied as 250 mg. soft gelatin capsules in bottles of 100.

Schering CORPORATION
BLOOMFIELD, N. J.

*T.M. †U.S. Pat. Pending

DORMISON

for the new diabetic

Globin Insulin 'B.W.&Co.'®

In the recently established case of diabetes, it is often advantageous to stabilize the patient with intermediate acting Globin Insulin.
Most mild and many severe cases can be controlled with a single injection daily.

A clear solution, it permits accurate measurement of doses.

When Globin Insulin is given before breakfast the peak of action occurs in the late afternoon, when it is conveniently balanced by distribution of the carbohydrate in the diet.

'Wellcome'® brand Globin Insulin with Zinc.

In vials of 10 cc., 40 units or 80 units per cc.

Burroughs Wellcome & Co. (U.S.A.) Inc., *Tuckahoe 7, N. Y.*

No fish-oil taste or burp

New Multivitamin Tablet Contains Synthetic Vitamin A . . .

Plus B_{12} . . . PLUS 7 OTHER IMPORTANT VITAMINS

Even finicky patients like DAYALETS, the fishless, burpless multivitamin tablets. No fish-oil odor, taste or aftertaste, no allergies due to fish oils—because they contain no fish oil.

Small and easy to swallow, these hard, compressed tablets can't leak, won't stick together in the bottle. DAYALETS are better tolerated by patients than soft gelatin capsules. Vanilla flavored and sugar coated. In bottles of 50, 100 and 250. Abbott

Each DAYALET tablet contains:

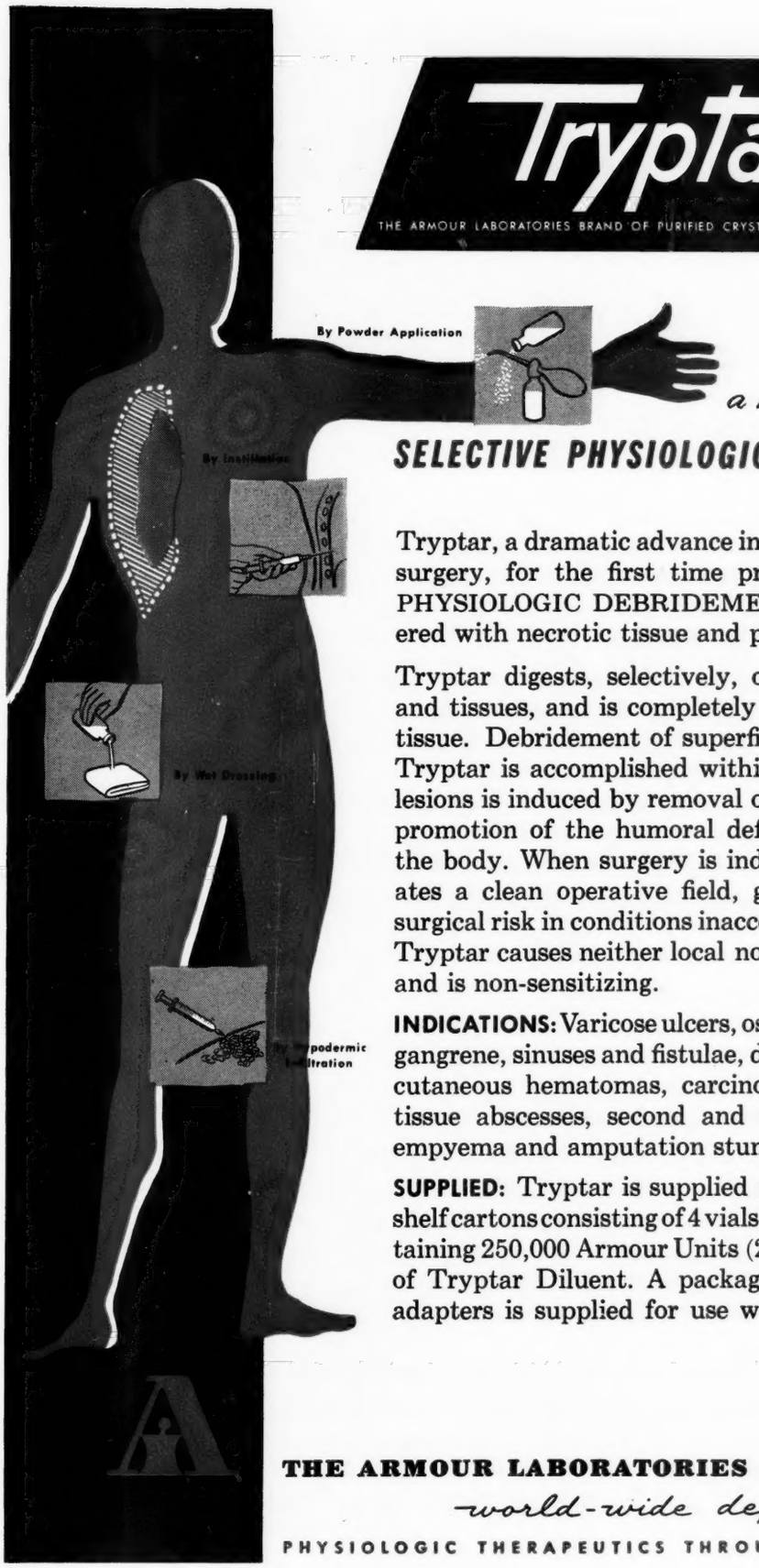
Vitamin A	10,000 U. S. P. units (synthetic vitamin A palmitate)
Vitamin D (Viosterol)	1000 U. S. P. units
Thiamine Mononitrate	5 mg.
Riboflavin	5 mg.
Nicotinamide	25 mg.
Pyridoxine Hydrochloride	1.5 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	1 mcg.
Pantothenic Acid (as calcium pantothenate)	5 mg.
Ascorbic Acid	100 mg.

NO FISH-OIL TASTE OR BURP

Dayalets

TRADE MARK

(ABBOTT'S MULTIPLE VITAMINS)



Tryptar

THE ARMOUR LABORATORIES BRAND OF PURIFIED CRYSTALLINE TRYPSIN

a new agent for

SELECTIVE PHYSIOLOGIC DEBRIDEMENT

Tryptar, a dramatic advance in general practice and surgery, for the first time provides SELECTIVE PHYSIOLOGIC DEBRIDEMENT of surfaces covered with necrotic tissue and pyogenic membranes.

Tryptar digests, selectively, only non-viable cells and tissues, and is completely innocuous for living tissue. Debridement of superficial ulcerations with Tryptar is accomplished within hours. Healing of lesions is induced by removal of local obstacles and promotion of the humoral defense mechanisms of the body. When surgery is indicated, Tryptar creates a clean operative field, greatly reducing the surgical risk in conditions inaccessible to antibiotics. Tryptar causes neither local nor antigenic reactions and is non-sensitizing.

INDICATIONS: Varicose ulcers, osteomyelitis, diabetic gangrene, sinuses and fistulae, decubitus ulcers, subcutaneous hematomas, carcinomatous ulcers, soft tissue abscesses, second and third degree burns, empyema and amputation stumps.

SUPPLIED: Tryptar is supplied in One-Million-Unit shelf cartons consisting of 4 vials of Tryptar, each containing 250,000 Armour Units (250 mg.), with 4 vials of Tryptar Diluent. A package containing plastic adapters is supplied for use with powder blowers.

THE ARMOUR LABORATORIES • CHICAGO 11, ILLINOIS

world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

more effective[1-6]
than ferrous sulfate

better tolerated[2-7]
than ferrous sulfate

White's **mol-iron**®

—a co-precipitated complex of ferrous sulfate and molybdenum sesquioxide: the most effective iron therapy known—in comparison to ferrous sulfate or other iron salts.

1. *Dieckmann, W. J. and Priddle, H. D.: Am. J. Obstet. & Gynecol.* 57:*541 (March) 1949.*
2. *Chesley, R. F. and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp.* 1:*68 (Sept.) 1948.*
3. *Healy, J. C.: J. Lancet* 66:*218 (July) 1946.*
4. *Neary, E. R.: Am. J. Med. Sc.* 212:*76 (July) 1946.*
5. *Talso, P. J.: J. Insurance M.* 4:*31 (Dec.-Jan.-Feb.) 1948-49.*
6. *Forman, J. B.: Conn. State M. J.* 14:*930 (Oct.) 1950.*
7. *Kelly, H. T.: Penn. M. J.* 51:*999 (June) 1948.*

Tablets • Liquid • Drops • Capsules with calcium and vitamin D
Capsules with liver and vitamins (including B_{12})

White Laboratories, Inc., Kenilworth, N. J.

It's Effective
It's "Patient-Accepted"

Wyeth®

- The pleasant candy-like flavor of Pondets gains immediate patient acceptance and cooperation. Especially important to the physician, Pondets offer *improved* intraoral therapy because:

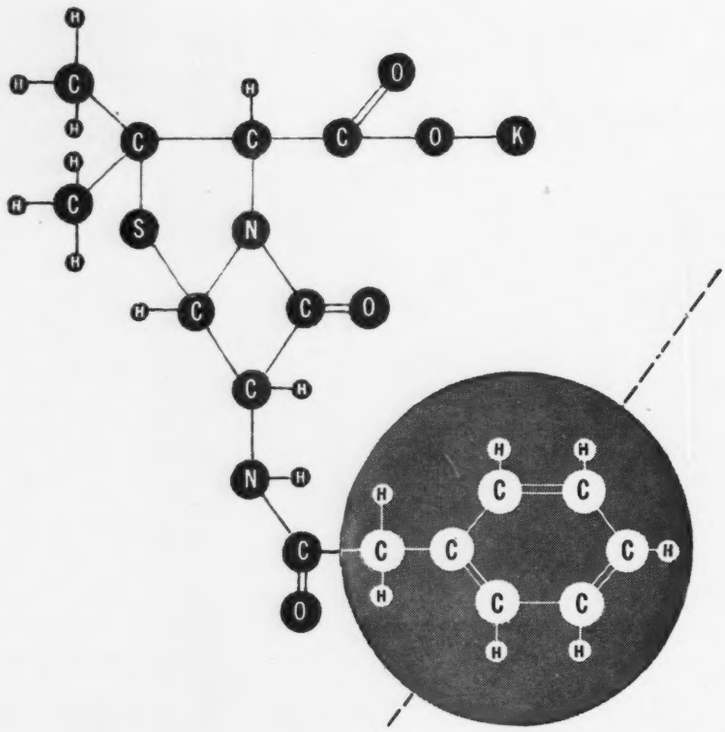
  - Each troche contains 20,000 units of penicillin and 50 units of bacitracin in synergistic combination.
  - Combined antibiotic therapy minimizes danger of bacterial drug resistance.
  - High, effective saliva levels of the combined antibiotics persist for at least one-half hour.

PONDETS®

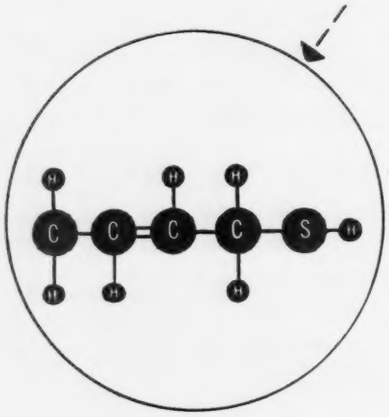
PENICILLIN-BACITRACIN TROCHES, WYETH

SOLD ON PRESCRIPTION ONLY

Wyeth Incorporated, Philadelphia 2, Pa.



10 years old and a change for the better



The 10th anniversary of the clinical use of amorphous penicillin is fittingly marked by the introduction of a new and improved crystalline compound, one that is usually well tolerated even by penicillin G (benzyl penicillin) sensitive patients –

Cer-O-Cillin *

(ALLYLMERCAPTOMETHYL PENICILLIN)

The replacement of the benzyl by an allyl-mercaptomethyl group is a "change for the better"

1. Affording a lower incidence of allergic reactions.
2. Enabling continued penicillin therapy of most G-reactive patients, and
3. Permitting a majority of G-sensitive individuals to resume penicillin G *without reaction*—after a course of Cer-O-Cillin.

*Trademark

A product of

Upjohn

Research

for Medicine... Produced with care... Designed for health

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Complete and lasting relief to 90% of patients with

nausea and vomiting of pregnancy

A recent clinical study[1] finds 'Dexedrine' remarkably effective in the treatment of the nausea and vomiting of pregnancy.

The author states:

1. "In a series of 165 patients with nausea and vomiting of pregnancy, 'Dexedrine' Sulfate produced complete relief in 148, or 90% .... Marked improvement occurred in almost every case within three days .... Complete relief occurred in four to ten days."

2. "'Dexedrine' has definite advantages over other treatments, most important of which are the mental and physical alertness, and the general feeling of well-being which it produces."

The study concludes: 'Dexedrine' "usually gives prompt and lasting relief; it is effective orally; it produces no significant side effects; and it gives mental and physical stimulation which improves the patient's morale and enables her to carry on normal activities."

Smith, Kline & French Laboratories, Philadelphia

Dexedrine* tablets & elixir

the antidepressant of choice and the most effective drug for control of appetite in weight reduction

*T.M. Reg. U.S. Pat. Off.

1. Anspaugh, R. D.: Effects of Dexedrine Sulfate on Nausea and Vomiting of Pregnancy, Am. J. Obst. & Gynec. 60:888 (Oct.) 1950.

Ciba
Presents

A New Advance in Sulfonamide Safety ...

ELKOSIN®

BRAND OF SULFADIMETINE

Scored 0.5 Gm. tablets.
Bottles of 100 and 1000.

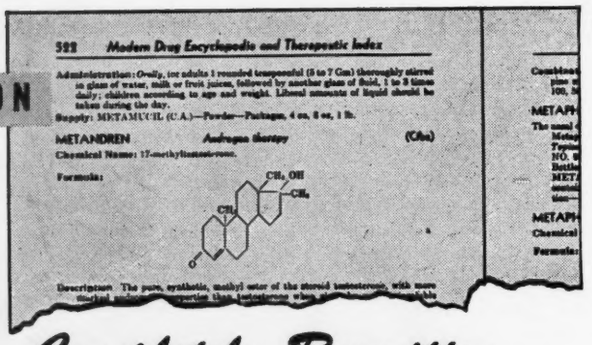
- Remarkably low incidence of side effects—less than 5%
- Lowest acetylation yet reported—less than 10% in blood
- New improved solubility
- Renal complications rare—alkalis not needed
- High, sustained blood levels

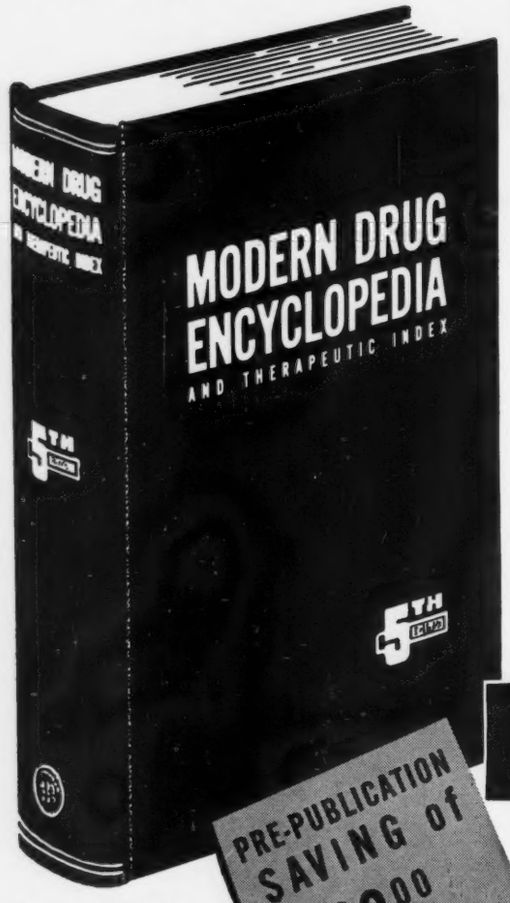
WIDE ANTIBACTERIAL SPECTRUM

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J. 2-1090 M

NEW 5TH EDITION

COMING EARLY 1952





Bound in Red Fabricoid. 1200 pages, size 6" x 9¼" x 2¼" Pre-Publication Price, Postpaid $12* U.S.A. $15 Foreign.

Completely Rewritten

to give you UP-TO-DATE Reference on nearly 4000 Ethical Drugs (including 1500 brand new listings) of 175 manufacturers.

Indispensable

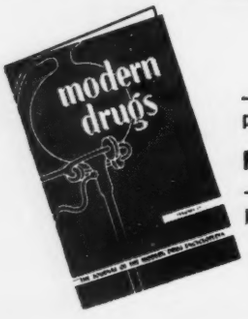
to PHYSICIANS for its authoritative, finger-tip data . . . complete from description to prescription. Now compiled in seven special sections: DRUGS • BIOLOGICALS • ALLERGENS • GENERIC NAME INDEX • THERAPEUTIC INDEX • MANUFACTURER'S INDEX • GENERAL INDEX. The new 5th Edition of The MODERN DRUG ENCYCLOPEDIA provides self-pronouncing drug listings for the first time.

Edited by
MARION E. HOWARD, M.D., F.A.C.P.
Yale University Medical School
New Haven, Conn.

PRE-PUBLICATION SAVING of $3.00 IF YOU ORDER NOW

MORE THAN 50,000 SATISFIED USERS

Saves hours of precious time. Proved by use as America's "best seller" medical encyclopedia.



FREE

—to every encyclopedia owner—

MODERN DRUGS

—the quarterly supplement that keeps you up-to-date with the newest drug descriptions.

MAIL THIS COUPON TODAY!

This Pre-Publication Saving Expires Feb. 1, 1952

DRUG PUBLICATIONS, INC.
49 West 45th Street, New York 19, N. Y.

Enclosed is the sum of twelve dollars ($12*. U.S.A.) for which please send me postpaid the new Fifth Edition of the MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX and MODERN DRUGS.

NAME_____ M.D.

ADDRESS_____

CITY_____ ZONE____ STATE_____

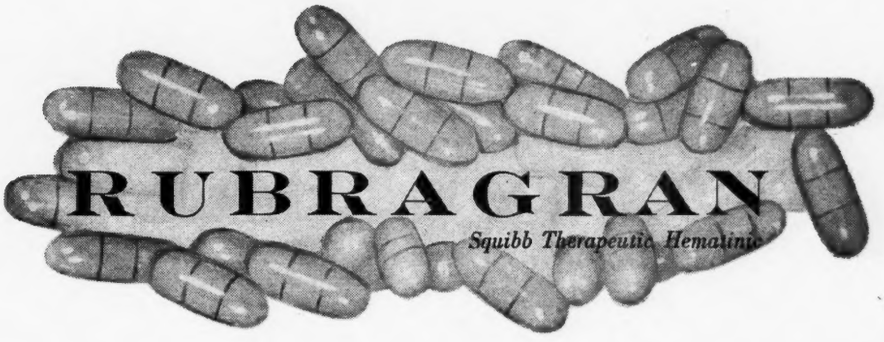
U.S.A. $12* FOREIGN $15

* Includes three-year supplementary service at $2 per year. (New York City residents please add 3% sales tax.)

MN

NEW!

an oral therapeutic hematinic



IN RECOMMENDED DOSAGE — 1 capsule t.i.d. — Rubragran supplies *truly therapeutic amounts* of four fundamental factors in normal red blood cell production.

RUBRAGRAN FORMULA	1 capsule supplies	1 capsule t.i.d. supplies
Vitamin B_{12}	25 mcgm.	75 mcgm.
Folic Acid	1.67 mg.	5 mg.
Ascorbic Acid	100 mg.	300 mg.
Iron (elemental)	67 mg.	200 mg.
(as ferrous sulfate exsic.)	230 mg.	690 mg.
Desiccated Liver	100 mg.	300 mg.

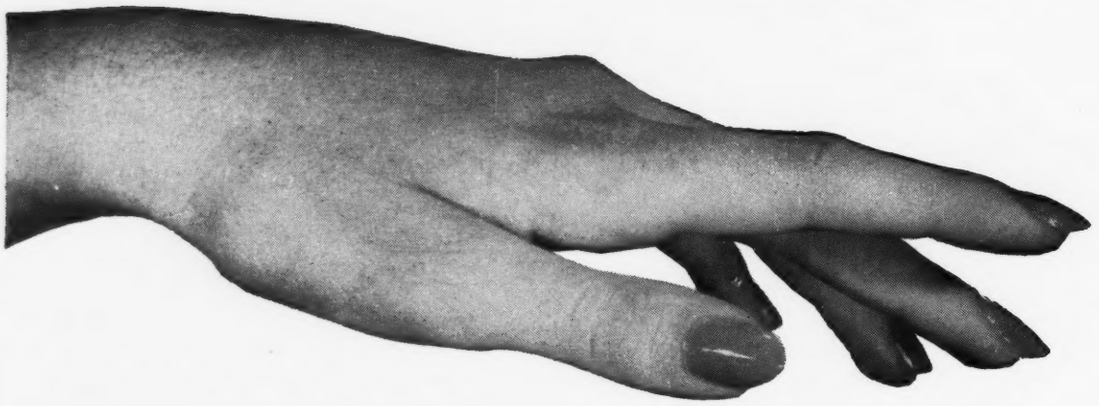
Bottles of 100 and 500

Because of the serious nature of the disease, true addisonian pernicious anemia should not be treated with oral preparations. Parenteral Rubramin or Liver Injection should be used.

SQUIBB

From Youth to Age

Benzestrol Covers Your Estrogenic Problems

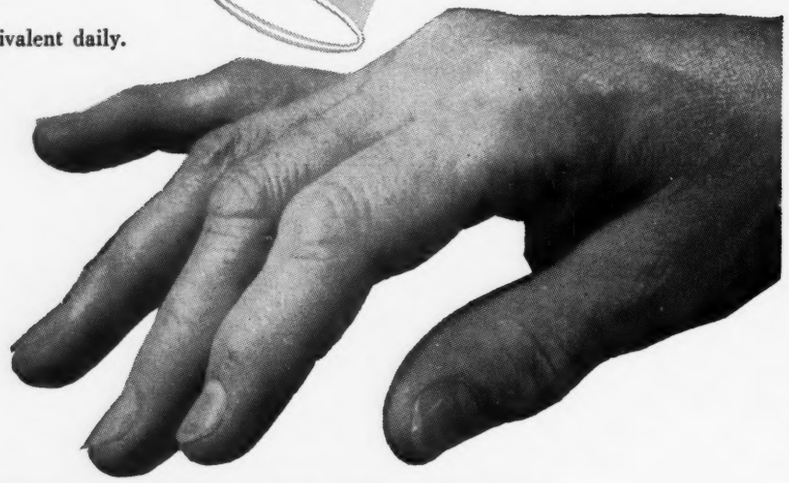


"Benzestrol, in my experience, provides prolonged beneficial effects . . . . Undesirable side reactions, . . . were not encountered in my experience . . . In general also there seemed to be quite a decided improvement in the vague arthropathies and hypertensions associated with the menopausal syndromes."*

The Effective, Non-toxic, Synthetic Estrogen
Available in all Dosage Forms:

Oral Tablets: 0.5 mg., 1.0 mg., 2.0 mg., 5.0 mg.
Vaginal Tablets: 0.5 mg.
Injectable Solution: 5.0 mg. per cc.
Elixir: 2.0 mg. per teaspoonful.
Average Dose: 1 to 2 mg. or equivalent daily.

*Hufford, A.R.: J.A.M.A., *123*, 259, (1943)



ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

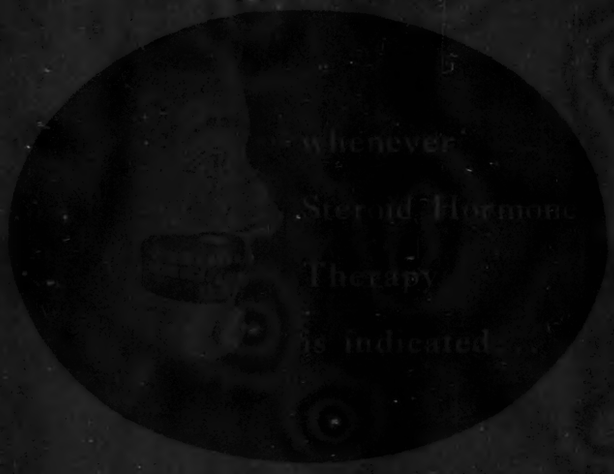
Schieffelin **BENZESTROL**

2, 4 - di (p - hydroxyphenyl) - 3 - ethyl hexane
Clinical abstracts, literature and samples on request.

Schieffelin & Co.
24 Cooper Square, New York 3, N. Y.

Advertisers Index

November, 1951



LINGUETS

save time for the Physician[2]

save money for the Patient[1]

When placed in the natural pocket between gum and cheek, Linguets dissolve at a rate closely approximating that of absorption of the hormone by the oral mucosa. The drug passes directly into the systemic circulation and initial inactivation in the gastrointestinal tract and the liver is avoided. The efficiency of Linguets is augmented by their unique design. Shaped to fit securely and comfortably into the buccal pocket, they do not promote salivation and frequent swallowing.

The use of Linguets thus makes possible satisfactory therapeutic response with low dosages. "Manifestly, this represents a great financial saving to the patient . . ."[1] and "reduces the office load on the busy practicing physician."[2]

1. Rosenillo, R. F.: Am. Practitioner 2:425, March, 1949
2. Lisser, H., et al: Postgraduate Med. 6:359, November, 1949

Metandren®
LINGUETS
methyltestosterone
5 mg., white—10 mg., yellow

Lutocylol®
LINGUETS
anhydrohydroxyprogesterone
10 mg., yellow

***Eticylol®**
LINGUETS
ethinyl estradiol
0.5 mg., pink
*For treating prostatic carcinoma only

Percorten®
LINGUETS
desoxycorticosterone acetate
2 mg., green—5 mg., tan

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.